CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-251

STATISTICAL REVIEW(S)

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CLINICAL REVIEW(S)

CLINICAL AND STATISTICAL NDA REVIEW

NDA:	20-521
NAME OF DRUG:	Infasurf (Calf Lung Surfactant Extract Suspension)
INDICATION:	Respiratory Distress Syndrome
SPONSOR:	ONY, Inc.
SUBMITTED:	July 31, 1995
RELATED IND:	27,169

REVIEWERS

MEDICAL: L. Miriam Pina, M.D.

STATISTICAL: Antonis Koutsoukos, Ph.D.

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General Introduction

I. Material Utilized in Review

Three adequate and well-controlled studies were conducted to demonstrate the effectiveness of Infasurf in the prevention and treatment of RDS: two studies were considered pivotal: Study 9101 SCT-Prophylaxis Trial and Study 9101 SCT-Treatment Trial (both Infasurf-Exosurf), and one supportive of safety and efficacy , the ISCT-92 (Infasurf-Survanta). Additional experience with Infasurf in four uncontrolled clinical trials, Studies 8701, 8901, 8902, and 9303, investigated open-label use in about 14,000 infants.

Other submissions reviewed in this NDA are as follows, in the order they were submitted:

13/03/95, 30/06/95, 13/07/95, 27/07/95, 04/08/95, 21/08/95, 22/08/95, 21/09/95, 26/09/95, 16/10/95, 03/11/95, 06/11/95, 08/11/95, 01/12/95, 04/12/95, 15/12/95, 23/01/96, 08,02/96.

II. Background

1. Indication

The Sponsor, ONY, Inc., is seeking approval of Infasurf® (calf lung surfactant extract), for the prevention and treatment of Respiratory distress syndrome (RDS) in premature infants.

RDS is a major life-threatening illness in premature infants, characterized by a rapidly progressive respiratory failure, mostly due to a deficiency in pulmonary surfactant.

2. Other Related IND's and NDA's

NDA 20-044 - Exosurf, was approved in 1990, under orphan drug status, for the prevention and treatment of RDS in premature patients.

NDA 20-032 - Survanta, was approved in 1991, under orphan drug status, for the prevention and treatment of RDS in premature infants.

3. **Proposed Directions for Use.**

General

INFASURF should only be administered intratracheal through an endotracheal tube. The dose of INFASURF is 3 mL/kg of a 35 mg/mL suspension. The dose is drawn into a syringe from the single use vial using a 20 gauge or larger needle with care taken to avoid excessive foaming. Administration is made by injection of the INFASURF suspension into the airway.

Administration for RDS (initial and repeat doses)

Intratracheal administration can use either instillation through a catheter passed through the endotracheal tube and positioned at its distal end or instillation through a side port adapter into the endotracheal tube itself. Two attendants, one to instill the INFASURF, the other to monitor the patient and assist in positioning, facilitates the dosing.

If administration through a catheter placed in the endotracheal tube is selected, the administration is usually in 4 equal aliquots of 0.75 mL/kg with the catheter removed between each of the four instillations and ventilation restored for 0.5-2 minutes. Each of the four aliquots is administered in a different position, prone, supine, right and left lateral to facilitate even distribution of the surfactant.

If administration through the side port adapter is selected, the dose should be administered in two aliquots of 1.5 mL/kg. One aliquot is instilled with the infant positioned with the right side dependent and the other with the left side dependent. Administration is made while ventilation is continued over 20-30 breaths for each aliquot with a small burst timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots.

Repeat Doses

Automatic repeat doses, up to a total of 3, 12 hours apart have been given in the INFASURF controlled pivotal clinical trials if the patient was still intubated.

4. **Foreign Marketing**

Infasurf has not been approved yet in any country.

III. Chemistry

Infasurf is an off-white suspension of calf lung surfactant extract in 0.9% sodium chloride solution. Calf Lung Surfactant Extract (CLSE), is a complex biological mixture of lipid and protein moieties of natural lung surfactant

Each mL of Infasurf contains:

35 mg total phospholipids (including ≥ 19 mg phosphatidylcholine) and 0.5 to 1.2 mg surfactant proteins SP-B and SP-C.

Description of Clinical Trials

The main sources of data to support efficacy and safety of Infasurf reviewed in this NDA are:

a. 2 active controlled pivotal trials:
   - SCT-P: 853 infants received prophylaxis therapy. Infasurf vs. Exosurf.
   - SCT-T: 1,126 infants received rescue treatment. Infasurf vs. Exosurf.

b. 1 active controlled supportive trial:
   - ISCT-92: 1,119 infants received prophylaxis or rescue therapy. Infasurf vs. Survanta.

c. 4 uncontrolled studies:
   - 8701: 13,278 infants received rescue or prophylaxis therapy
   - 8901: 500 infants randomized to treatment of moderate disease vs. severe disease
   - 8902: 1,398 infants randomized to rescue vs. prophylaxis
   - 9303: 197 infants treated in an open label, not randomized, interim study of rescue vs. prophylaxis

CONTROLLED, PIVOTAL STUDIES: SURFACTANT COMPARISON TRIAL (SCT) INFASURF VS. EXOSURF.

I. PROPHYLAXIS TRIAL (SCT-P)

1. Trial Officers and Investigational Centers:

A. Principal Investigator: **Mark L. Hudak, M.D.**
State University at Buffalo, NY

B. Sponsor: **Edmund A. Egan, M.D.**
President & Medical Director,
ONY, Inc.

C. Participating Centers: **10 centers**

2. Objective
To determine the differences in efficacy between Infasurf and Exosurf in the prevention of Respiratory Distress Syndrome in Premature infants. The secondary objective was to assess the safety profile of Infasurf compared to that of Exosurf.

3. Study Design
Phase III, multicenter, randomized, masked, active control, parallel study.

4. Inclusion Criteria
A. Gestational age ≤ 28 weeks,
B. Birth weight ≤ 1,100 grams.

Reviewer's note: Even though the protocol included a birth weight limit in the entry criteria, later on, patients with BW>1,100 grams were enrolled in the study.

5. Exclusion Criteria
A. Severe congenital anomalies,
B. Congenital septicemia (from blood or CSF samples taken within the first 24 hours of birth),
C. Clinical chorioamnionitis,
D. Rupture of fetal membranes> 14 days with oligohydramnios.

Reviewer's note: The last 3 criteria were later changed to a category of "High risk factors" but were not in the exclusion criteria . This change (and its rationale) to the protocol was not submitted to, nor approved by, this agency. We subsequently analyzed the incidence of RDS excluding the patients that met c. and d. of the exclusion criteria to determine if this change in the protocol would have any impact in the results.

6. Blinding and Administration of Surfactant

A. Infants were randomized in the delivery room after birth. The assigned surfactant was prepared in a private area, and administered by a nurse who would not participate directly in the primary care of the infant for at least 5 days. This nurse was appointed at the beginning of every shift. She was assisted by 2 experienced neonatal resuscitators in the positioning and monitoring of the infant during the administration of the surfactant.

Reviewer's note: For the administration of surfactant, the sponsor claims that all the centers decided to use protocol B which instructed to have a team consisting of: 2 neonatal resuscitator experts and a nurse administrator of the surfactant. The protocol does not explicitly preclude these 2 experts from taking direct care of the patient (Appendix 7, vol 29). The nurse administrator was required to abstain from taking direct care of the treated infant for at least 5 days. Infasurf (3 ml/kg of 35 mg/ml of phospholipids) was given with a side port adapter in two aliquots, the same as Exosurf (this was given 5 ml/kg).

B. Exosurf and Infasurf doses were given the same way. The dose was divided in 2 equal aliquots, and given through a side port adapter. Each aliquot was given in small bursts during the inspiration cycle. After each aliquot was given the infant was moved to either the right or the left side, and then repositioned to the midline.

C. Dosages. - For Infasurf: 3 ml/kg body weight
For Exosurf: 5 ml/kg body weight.
This dose was repeated up to a total of 3 doses every 12 hours if the patient was still intubated.

Reviewer's note: The protocol allowed the site investigators to deviate from the protocol when deemed necessary. Study medication could be withheld after any dose, if in the opinion of the investigator the infant did not need treatment any more.

D. Crossover.
Infants who completed surfactant prophylaxis treatment and persisted with a/A PO2 < 0.10 on two consecutive ABG's

received crossover treatment. This treatment followed the procedure for rescue treatment, two total doses 12 hours apart, each dose divided in two equal aliquots.

7. Endpoints

A. Primary Efficacy Measures:
- Incidence of RDS
- Incidence of BPD, and
- Mortality secondary to RDS.

B. Secondary Efficacy and Safety Measures:
- Total respiratory mortality [early (<7 days) and late (>7 days)].
- Total neonatal mortality (at 7 and 28 days) includes respiratory and nonrespiratory deaths
- Severity of RDS
- Incidence of RDS-related air leaks
- Incidence of crossover surfactant treatment
- Incidence of acute pulmonary hemorrhage
- Severity of BPD.

C. Other Safety Endpoints:
- Incidence and severity of IVH
- Complications of prematurity
- Adverse events

8. Statistical Analysis

A. The sample size of 400 subjects was calculated to detect a 20% decrease in the incidence of RDS in the Infasurf treated group, from a 68% incidence estimated in the Exosurf treated group, with a two sided $\alpha=0.05$ and an 80% power.

B. The primary efficacy variables were analyzed using a logistic regression model including the factors of treatment, center and treatment by center interaction. Treatment by center interaction was dropped from the model because the interactions were either statistically not significant or the model did not fit. Whenever the model did not fit, the Fisher's exact two-tailed test for a 2x2 contingency table was used. The centers that had 10 or fewer patients within either treatment group, within the target birth weight group, were combined into one center. The CATMOD (categorical data modeling) procedure of SAS was used to fit the logistic regression model.

C. All p-values associated with qualitative variables in this review are obtained from the CATMOD procedure (where the logistic regression model is fit to the data), unless it is indicated otherwise. P-values associated with quantitative variables are obtained from the t-test. Statistical significance was declared if two-sided p-value was ≤0.05.

9. Results

A. Demographic Characteristics

(1) Neonatal Demographics
A total of 871 patients were randomized, of those, 853 infants received test drug treatment. 18 patients did not receive any study medication because, after delivery, they were thought to not meet the entry criteria. In the ITT population 5 of the 18 patients had been randomized to the Infasurf group and 13 to the Exosurf group. (See TABLE 1 for the distribution of patients).

TABLE 1. Total distribution of patients entered.

Treatment	ITT Population N=871		TBW Population (700-1100 g) N=492	
	Infasurf	Exosurf	Infasurf	Exosurf
Total Randomized	436	435	253	239
Total Rz and treated	431	422	250	237
Total Rz and not treated	5	13	3	2
p-Value*	0.06		1.0	

*Fisher's two-tailed test

Neonatal demographic information consisting of birth weight, gestational age, sex, race, number of multiple births, cord pH, and Apgar scores were evaluated. There

were no statistically significant differences in the demographic characteristics of both treatment groups.

Reviewer's note: Table 4.7 page 08-0479 vol 27 of the submission, tabulates total patients randomized *and* treated as if there were 436 treated in the ITT population and 253 in the TBW population in the Infasurf group, and 435 and 239 in the ITT and the TBW population respectively, in the Exosurf group, and not as is presented in our above table. The sponsor has acknowledged this error in their table.

(2) Number of Patients per Birth Weight.
Even though the protocol only called for inclusion of patients of a birth weight ≤ 1100 g., there were 177 extra patients treated, with BW outside the target weight. See their distribution in table 2.

Table 2. Distribution of infants per birth weight.

Population	Not treated (N= 18)	Infasurf (N= 431)	Exosurf (N= 422)	Row Summary (N= 871)
< 700 g	7	98	97	202
> 1100 g	6	83	88	177
700-1100 g	5	250	237	492

(3) Obstetrical Demographics
The following pregnancy-related variables were recorded: prenatal steroids, tocolysis, labor, rupture of membranes > 1 hour, chorioamnionitis, C-section, abruptio placentae, placenta previa, gestational diabetes, insulin-dependent diabetes, preeclampsia, and oligohydramnios > 14 days. There were no significant statistical differences within the two groups.

Reviewer's note: Even though the protocol excluded infants with the above criteria, 237 infants with maternal history of either oligohydramnios > 14 days, chorioamnionitis, and/or congenital sepsis, or where the condition was unknown, were later on included in this trial. One hundred and fifteen infants meeting one or more of these exclusion criteria were included in the Infasurf group and 122 in the Exosurf group. Statistically significantly more ineligible patients developed RDS in the Exosurf group than in the Infasurf group (33% vs 17%, p=0.004). Table 3 shows the incidence of RDS in the group of infants meeting one or more of the exclusion criteria included in the study. In a later analysis (TABLE 7), the incidence of RDS was evaluated excluding these patients. Infasurf continued to have significantly less incidence of RDS than Exosurf. TABLE 4 shows the distribution of the ineligible patients by birth weight.

Table 3. Number of patients (Percentage) initially not eligible to participate in the study, by Dx of RDS.

Treatment	RDS	No RDS	Indeterminate
Exosurf (n= 122)	40 (33%)	70 (57%)	12 (10%)
Infasurf (n=115)	19 (17%)	86 (75%)	10 (9%)
p-value*	0.004	0.006	0.825

*Fisher's two-tailed test

TABLE 4. Patients initially not eligible to participate in the study by birth weight. Number of patients.

Birth weight group	Infasurf (N= 115)	Exosurf (N=122)	p-value*
< 700 g	28	24	0.434
700 - 1100 g	70	63	0.19
> 1100 g	17	35	0.012

*Fisher's two-tailed test

B. Efficacy Results

(1) Incidence of RDS

- **Infants were considered to have RDS if they had a CxR consistent with RDS (reticulo-granular infiltrates with or without an air bronchogram effect) between 16 and 32 hours of age *and* a FiO2 ≥ 30%.**

- **Infants were considered to have NO RDS if the infant was on < 30% O2 at the time the CXR was**

taken if within 16 to 32 hours of life. Infants were considered to have NO RDS, if the CXR was taken out of the 16 to 32 hours period, but the FiO2 at 26 hours was <30%.

+ **Infants were considered indeterminates if :**
  - **no O2 information at 24 or 26 hours was available;**
  - **CxR was indeterminate and FiO2 was ≥30%;**
  - **CxR was taken at <16 or >32 hours of age, except in the cases where the infant died before 16 hours of age. In these cases, the last CXR taken before the infant died was evaluated.**

TABLE 5 shows a summary of the criteria used in the definition of RDS.

TABLE 5. Definition of RDS

Diagnosis	CXR at 16 - 32 hrs	FiO2 at time CXR was taken
RDS	Positive changes	≥ 30%
No RDS	Positive, or indeterminate	<30%
	If CXR was not taken at 16 - 32 hours, but	FiO2 at 26 hours was <30%
Indeterminate	Absent or indeterminate, or taken outside the 16 - 32 hrs.	≥ 30%
	Positive, absent or indeterminate	not available

The incidence of RDS (at 16 - 32 hours) was significantly lower ($p<0.001$) for Infasurf-treated infants than for Exosurf-treated infants in both the ITT and TBW populations (ITT – 15.3% vs 47.0% , TBW – 15.5% vs. 43.9%). The incidence of RDS for patients outside the TBW population (<700 g and >1100 g) is significantly lower in Infasurf-treated patients than in Exosurf-treated patients ($p<0.001$). When analyzed by study site,

Infasurf-treated patients also had a lower incidence of RDS in the ITT population than Exosurf-treated patients. In 8 of 10 centers the difference was statistically significant. Within the TBW population, only 4 of the 10 centers had a statistically significantly lower incidence of RDS in the Infasurf treated group than in the Exosurf group. The incidence of RDS by birth weight and treatment group is presented in TABLE 6.

TABLE 6. **Incidence of RDS by birth weight and treatment group. Number/total (Percentage).**

Treatment	ITT	TBW	< 700 g	>1100 g
Infasurf	62/406 (15.3%)	36/233 (15.5%)	23/94 (24.5%)	3/79 (3.8%)
Exosurf	183/389 (47.0%)	97/221 (43.9%)	61/90 (67.8%)	25/78 (32.1%)
p-value	<0.001	<0.001	<0.001	<0.001*

Note: The sponsor chose to report very small p-values as being "<0.001".

Reviewer's note: The denominators of the above table represent the number of infants that by definition were evaluable for RDS, i.e., as the sponsor explained in an amendment to the NDA of August 29, 1995: infants with available and readable CXR taken at 16 to 32 hrs of age and read by the study center, and an available record of the FiO2 required by the patient at the time the CXR was taken or at 26 hrs of age. In total, there were 58 patients considered indeterminates (25 patients in the Infasurf group and 33 in the Exosurf group). The following are the reasons presented by the sponsor by which the 58 patients were not included in the evaluation of RDS:

1. Diagnostic CXR was taken outside the required 16 to 32 hrs of age AND FiO2>30%.
   Infasurf = 17 infants
   Exosurf = 20 infants

2. Diagnostic CXR not read at Study Center AND FiO2 >30%
   Infasurf = 6 infants
   Exosurf = 7 infants

3. Diagnostic CXR not read at Study Center and patient died <24 hrs of

cause other than RDS
Infasurf = 1 infant
Exosurf = 3 infants

4. Diagnostic CXR indeterminate in itself AND FiO2 >30%
Infasurf = 1 infant
Exosurf = 3 infants

This reviewer considers noteworthy the following comments:

1. Following the sponsor's above parameters of indeterminates, we reassessed those patients classified as with RDS and found that there were 19 infants (16 infants in the Exosurf group and 3 in the Infasurf group) with the diagnostic CXR taken outside the required time frame and FiO2 >30%. All these infants had died at less than 24 hours of age.
2. There are 10 patients (3 in the Exosurf group, and 7 in the Infasurf group) classified as NO RDS where the FiO2 is >30% and the CXR was taken outside the specified time frame. In these cases the FiO2 at 26 hours was <30% and the patient was considered without RDS.
3. The patients with ID#'s 11-05060 and 11-01107 were classified as RDS Indeterminates because, as explained in the August 29,1995 amendment, the diagnostic CXR was not read at Study Center and the patients died <24 hrs of age of "a cause other than RDS". However, these two patients were included in the count of RDS deaths in the Exosurf treated group. These patients should not be counted as RDS death for Exosurf.
4. Patient ID# 11-01146 was classified as RDS Indeterminate because of "Diagnostic CXR taken outside the required time frame (14 hours) with a FiO2 >30%." This patient died at 1.9 days of age and was counted as RDS death in the Exosurf treated group. It is difficult to believe that a patient who died at almost 28 hours of age, did not have any other CXR taken after 14 hours of age. This patient should not be counted as RDS death for Exosurf.
5. Patient 11-01150 in the Infasurf group, had the CXR taken at the proper time and it was read as with chronic changes. This patient was classified as indeterminate and should have been classified as with NO RDS.
6. More patients in the Exosurf group who met one or more of the exclusion criteria (oligohydramnios > 14 days, maternal history of chorioamnionitis, and/or congenital sepsis) developed RDS (33% vs. 17%, p=0.004).

Modified analysis of the incidence of RDS in a worse case scenario

To assess the impact of the infants with RDS indeterminate, and of those meeting one or more of the original exclusion criteria, on the global incidence of RDS, we analyzed the RDS data in the worse case scenario, i.e., the most conservative way:

1. All the indeterminates for the Infasurf group were considered as with RDS and all the indeterminates for the Exosurf group as with NO RDS.
2. Those infants with oligohydramnios >14 days, maternal Hx. of chorioamnionitis and congenital sepsis were excluded from the analysis. (There were 115 patients in the Infasurf group and 122 patients in the Exosurf group meeting one or more of these criteria. See TABLE 3 for distribution of these infants by treatment and RDS diagnosis).

In summary, the number of patients originally eligible to participate in the study, by diagnosis of RDS, is as follows:

	RDS	NO RDS	Indeterminates
Infasurf (N=316):	43 (14%)	259 (82%)	14 (4%)
Exosurf (N=300):	143(48%)	136 (45%)	21 (7%)

TABLE 7 presents the modified incidence of RDS by birth weight, in the worse case scenario. Each record was reviewed in terms of meeting the inclusion, exclusion and RDS criteria. In this analysis, the Infasurf-treated patients still had a statistically significantly lower incidence of RDS than the Exosurf group (p=<0.0001).

TABLE 7. Modified incidence of RDS in the worse case scenario. Number/total of patients.

Treatment	ITT	TBW	< 700 g	>1100 g
Infasurf	57/316 (18 %)	33/180 (18%)	20/70 (29%)	4/66 (6%)
Exosurf	143/300 (48%)	77/174 (44%)	48/73 (66%)	18/53 (34%)
p-value	<0.0001	<0.0001	<0.0001	<0.0005

See text above for an explanation of the denominators.

(2) Incidence of BPD

The incidence of BPD was defined by oxygen dependence and the Edwards-Toce X-ray Score ≥ 4 at 28 days. Infants who survived to 28 days without occurrence of BPD were defined to have intact cardiopulmonary (CP) survival.

EDWARDS-TOCE X-RAY SCORE
The five parameters below, evaluated in CXR's for BPD diagnosis, were scored as normal (0), mildly or moderately abnormal (1), or markedly abnormal (2).

- **cardiovascular abnormalities,**
- **hyperexpansion,**
- **emphysema,**
- **fibrosis or interstitial abnormalities, and**
- **overall subjective appearance of radiograph.**

There were no statistically significant differences between treatment groups either for the ITT , or any of the birth weight subsets. See TABLES 8 and 9.

TABLE 8. Incidence of BPD - ITT and TBW populations. Number/total (percentage) of patients.

Parameter	ITT population (N=853)			TBW population (700 - 1100 g) (N=487)		
	Infasurf (N=431)	Exosurf (N=422)	p-value	Infasurf (N=250)	Exosurf (N=237)	p-value
Intact CP survival[a]	318/431 (74%)	292/422 (69.2%)	0.15	193/250 (77.2%)	173/237 (72.9%)	0.30
BPD[b]	61/376 (16%)	62/354 (17.5%)	0.60	42/234 (18%)	35/208 (16.8%)	0.95

[a] Defined as infants who survived and do not have BPD at 28 days.
[b] Denominators indicate survivors with data

TABLE 9. Incidence of BPD -Number/total (percentage) of Patients -Patients under 700 g and over 1100 g of birth weight.

Parameter	Population: < 700 g BW (N=195)			Population: > 1100 g BW (N=171)		
	Infasurf (N=98)	Exosurf (N=97)	p-Value	Infasurf (N=83)	Exosurf (N=88)	p-Value
Intact CP survival[a]	50/98 (51.0)	46/97 (47.4)	0.67	75/83 (90.4)	73/88 (83.0)	0.18
BPD[a,b]	17/57 (29.8)	19/59 (32.2)	0.85	2/27 (7.4)	8/39 (20.5)	0.15

[a] Defined as infants who survive and do not have BPD at 28 days
[b] Denominators indicate survivors with data
[a] Receiving O_2 at 28 days and positive chest radiograph

(3) Mortality Secondary to RDS (death at ≤14 days of age)

Mortality secondary to RDS was defined as death primarily due to RDS and its complications, that occurred at or before 14 days and was not associated with culture positive sepsis/ pneumonia, or with pulmonary hypoplasia. Data were analyzed according to assignments made at individual study sites and also according to assignment made at the central coordinating committee (CCC) based on the interpretation of the CxR made by the Radiology reading center (RRC). In case of a difference between the study site and the CCC, the Steering Committee decided the final "cause of death". See TABLE 10 for mortality secondary to RDS by place of determination.

When assessing the infants weighing outside the TBW, there were no statistically significant differences between treatment groups in the incidence of death due to RDS. This was true at the individual study sites and at the central level.

TABLE 10. Mortality secondary to RDS by place of determination. Number (Percentage) of patients. ITT and TBW groups

RDS Death	ITT Population			TBW Population		
	Infasurf (N=431)	Exosurf (N=422)	p-value	Infasurf (N=250)	Exosurf (N=237)	p-value
Study sites	9 (2.1)	18 (4.3)	0.08	1 (0.4)	5 (2.1)	0.11
Committee	7 (1.6)	23 (5.5)	0.004	0 (0.0)	8 (3.4)	<0.01

*** The 95% Confidence Interval for difference between treatment group percents was 2.2 ± 2.4 (ITT Population) and 1.7 ± 2.0 (TBW Population) at the study sites, and 3.9 ± 2.5 (ITT Population) and 3.4 ± 2.3 (TBW Population) at the central committee.**

Reviewer's Note: The original cause of death was assigned by the principal investigators (PI's) at each study site. These assignments were reviewed by the CCC. When the CCC did not agree with the PI's assignment, the CCC would try to reach an agreement by disclosing the pre-determined definitions of BPD and/or RDS to the PI's. If no agreement was reached, the final cause of death was determined by the Steering Committee, who was blinded to the treatment of the infants, but was familiar with the protocol. We reviewed the path followed by each final death assignment as recorded:

Exosurf group: Of the 18 original diagnoses of RDS given by the PI's as cause of death, 6 were changed to other diagnosis (2 IVH, 1 asphyxia, 1 BPD, 1 pulmonary hypoplasia, and 1 case considered non-viable). Of these 6 changes, 4 were made in patients of < 700 g. of BW, 1 >1100 g. and 1 in the TBW population. There was only one disagreement regarding these changes (a 28 weeks GA, female patient <700 gr. considered non-viable who died at 2 days of age). Of the 23 cases assigned by the CCC as RDS as cause of death , 10 were changed from the original diagnosis, plus one that did not have an original PI's diagnosis. Of the 11 changes, 6 were made to infants of <700 gr., 1 to >1100 gr., and 4 to the TBW population. There were 5 cases where the PI agreed with the changes recommended and 5 cases where the PI did not agree with the final assignment of RDS as a cause of death. From the last 5 cases, 2 cases were thought by the PI to be consistent with sepsis (ID #1115015 and 1110039), 1 case diagnosed as with pulmonary hypoplasia (ID #1112033, when autopsy results were requested, sponsor responded that it was not performed, infant died at 10 hrs of age, shortly after being placed on the jet ventilator. CXR consistent with RDS. He was not assessed as with any congenital anomalies.) and 2 cases that had "other" as a cause of death. Besides these cases, there was a case where the CCC diagnosed the cause of death as RDS and there was no diagnosis from the PI. These changes left a net increase of 5 RDS deaths in the ITT group, and a net increase of 3 RDS deaths in the TBW population (tables 4.14 and 4.15, page 46, vol 27, and data listing 6 of case report tabulations). After reviewing the clinical data, we found that the patients with ID#'s 11-05060 and 11-01107 were classified as RDS Indeterminates because, as explained in the August 29,1995 amendment, the diagnostic CXR was not read at Study Center and the patients died <24 hrs of age of "a cause other than RDS". However, these two patients were included in the count of RDS deaths in the Exosurf treated group. Patient ID# 11-01146 was classified as RDS Indeterminate because of "Diagnostic CXR taken outside the required time frame (14 hours) with a FiO2 >30%." This patient died at 1.9 days of age and was counted as RDS death in the Exosurf treated group. Patient with ID# 1110093 had a PI's cause of death as pulmonary hypoplasia, but the central committee assigned his death as RDS death. This child had Apgar scores of 0 at 1 min. and 5 at 5 min., on FiO2 of 100% at 26 hours and was assessed as with pulmonary hypoplasia in the congenital anomalies section. The above 4 patients should not be counted as RDS death for Exosurf.

In the Infasurf group: Of the 9 original cases where the PI had assigned RDS as a cause of death, the PI agreed to change it in the 2 instances were the Chair of the central committee recommended the change. One of the cases (ID# 1101134) was changed to BPD as a cause of death, as he died at 35 days of age; the second case (ID# 1101233) was determined to have IVH as a cause of death (he had grade 4 IVH, NO RDS established by CXR and was on 30% FiO2 at 26 hrs of age). The changes were agreed upon by the PI after learning the BPD and RDS definitions: BPD death (death at > 14 days) and RDS death (death at <14 days) set in the protocol; or after further discussion with the CCC.

The above changes rendered a statistically significant difference in mortality in favor of the Infasurf-treated patients, in both, the ITT and the TBW populations at the committee site. The sponsor claims that these changes were more likely to occur in the Exosurf group because of their increased incidence of RDS. The sponsor does not have written copy of the discussions followed at the Steering Committee when they were assigning the "final cause of death".

In conclusion, after reviewing the clinical data available from each individual, with the criteria of RDS death, and agreeing with the diagnosis of pulmonary hypoplasia as cause of death in case 11-10093 (without autopsy), we have the following results: for Infasurf, we agree with the changes made by the committee, presented in TABLE 10. For Exosurf, there were 19 cases of RDS in the ITT population, and 7 in the TBW. With these changes, there was a statistically significant difference in RDS mortality between both treatment groups in favor of Infasurf. TABLE 11 shows the modified incidence of mortality caused by RDS after our revision of the clinical data.

TABLE 11. Mortality secondary to RDS after revision of clinical data. Number (percentage) of patients.

	ITT Population			TBW Population		
	Infasurf (N=431)	Exosurf (N=422)	p-value	Infasurf (N=250)	Exosurf (N=237)	p-value*
RDS Death	7 (1.6)	19 (4.5)	0.016	0 (0.0)	7 (3)	0.006

*Fisher's two-tailed test

C. Secondary Efficacy And Safety Measures

(1) Total Respiratory Mortality

Total respiratory mortality is defined as all deaths of any respiratory cause, e.g., RDS and its complications, pulmonary hypoplasia, pneumonia, pulmonary hemorrhage, etc. that occurred to discharge. In the ITT and the TBW populations, statistically fewer deaths occurred in Infasurf treated patients than in Exosurf treated patients by both , the study site and the committee's determinations. See TABLE 12 for distribution of patients who died of respiratory causes by place of determination per treatment. For the subsets outside the TBW, there were no statistically significant differences between treatment groups in respiratory mortality per place of determination.

TABLE 12. Total respiratory Mortality by place of determination

Respiratory Mortality	ITT population			TBW Population		
	Infasurf (N=431)	Exosurf (N=422)	p-value	Infasurf (N=250)	Exosurf (N=237)	p-value
Study sites	20 (4.6)*	37 (9.0)*	0.03	5 (2.0)*	16 (6.7)*	0.02
Committee	22 (5.1)*	41 (9.7)*	0.01	7 (2.8)	16 (6.8)*	0.05

* Number of patients (Percentages).

Reviewer's note: The 95% CI for the difference between Infasurf and Exosurf in total respiratory mortality (-7.5, 0.8 sites; -8.1, -1.1 committee) indicate that Infasurf is doing better than Exosurf on this endpoint.

(2) **Neonatal Mortality**

Neonatal mortality is defined as all deaths, of any cause that occurred during the study period. It was totaled at 7 and 28 days and to discharge.

At 7 days: 31 (7%) infants died in the first 7 days of life in the Infasurf group and 47 (11%) in the Exosurf group (p=0.05)

At 28 days: there were 52 and 68 deaths in the Infasurf and Exosurf groups, respectively (p= 0.1). Twenty one infants died from 7 to 28 days in both groups.

At discharge, there were 77 deaths in the Infasurf group and 82 in the Exosurf group (p=0.56). Twenty five infants in the Infasurf group and 14 in the Exosurf group died between 28 days and discharge. TABLE 13 presents the number of infants who died per treatment group totaled at 7 and 28 days, and to discharge (from tables 4.14 and 4.15 vol 1.27).

TABLE 13. Neonatal Mortality per treatment group. Number (percent) of patients.

Overall Mortality	ITT population			TBW Population		
	Infasurf (N=431)	Exosurf (N=422)	p-value	Infasurf (N=250)	Exosurf (N=237)	p-value
7 days	31 (7)	47 (11)	0.05	8 (3)	19 (8)	0.04
28 days	52 (12)	68 (16)	0.10	15 (6)	29 (12)	0.03
To discharge	77 (18)	82 (19)	0.56	28 (11)	34 (14)	0.27

Reviewer's note: Infasurf-treated patients had a statistically significant decrease in the incidence of mortality when compared with Exosurf-treated patients at 7 days of age, in the ITT and TBW populations. There was also a statistically significant decrease in the incidence of mortality in the TBW group of Infasurf at 28 days of age. This significance was lost when mortality was assessed to discharge. From day 28 to day of discharge, the Infasurf group had an increase in mortality (32% vs. 18%). If we calculate the mortality rate (how many patients died related to how many patients where alive at the beginning of each period) the percentages at <7 days of age are better for the Infasurf-treated group than for the Exosurf-treated group (7% vs. 11%); at 7 to 28 days the percentages are about the same for both groups (5% vs. 5.5% for the Infasurf and the Exosurf-treated groups respectively); and for the period of 28 days of age to discharge, the Exosurf-treated group was slightly better than the Infasurf-treated group (4% vs 6.5%). We wanted to examine what was the cause of death of the patients who died between 28 days and discharge. The most common cause of death, as assigned by the committee, in the Infasurf group was not respiratory related: sepsis (9 cases), followed by BPD, necrotic enterocolitis and organ failure (4 cases each). In the Exosurf group, sepsis was the most common cause of death (5 cases), followed by organ failure (4 cases). There was no statistically significant difference in the rate of mortality when analyzed by age. The percent mortality by age did show statistical significance in favor of Exosurf in patients of 28 days and older. The cause of death of the infants who died from 28 days post birth to discharge are presented in TABLE 14. TABLE 15 shows mortality rate by age, and TABLE 16 shows the percent mortality by age.

TABLE 14. Cause of death from day 28 to discharge, by Treatment and site of assignment. Number (percentage) of patients.

Cause of death	Infasurf (N=25)		Exosurf (N=15)	
	Committee	Site	Committee	Site
Sepsis	9 (36)	8 (32)	5 (33)	5 (33)
BPD	4 (16)	1 (04)	2 (13)	1 (06)
Necrot. enterocolitis	4 (16)	4 (16)	1 (06)	1 (06)
IVH	2 (08)	2 (08)	1 (06)	0 (0)
Organ failure (liver, kidney)	4 (16)	4 (16)	4 (27)	2 (13)
Other	2 (08)	6 (24)	2 (13)	6 (40)

TABLE 15. Mortality rate by age. Number (percentage) of patients.

Age	INFASURF	EXOSURF	p-Value**
<7 days	31/431* (7)	46/422* (11)	0.0644
7 to 28 days	21/400* (5)	21/376* (5.5)	0.8453
28 days to D/C	25/379* (6.5)	15/355* (4)	0.1682

*Denominator is total patients alive at the beginning of each period.
**Fisher's two-tailed test

TABLE 16. Percent of Mortality by age. Number (percentage) of patients.

Age	INFASURF (N=77)	EXOSURF (N=82)	p-Value**
<7 days	31/77* (40)	46/82* (56)	0.057
<700 g	20	22	
TBW	8	20	
> 1100 g	3	4	
7 to 28 days	21/77* (27)	21/82* (26)	0.86
<700 g	11	10	
TBW	7	8	
>1100 g	3	3	
28 days to D/C	25/77* (32)	15/82* (18)	0.045
<700 g	10	8	
TBW	13	6	
>1100 g	2	1	

*Denominator is total infants who died in each treatment group.
**Fisher's two-tailed test

(3) Severity of RDS

The severity of RDS was calculated using an algorithm that utilized both the FiO2 and the mean airway pressure (MAP) over the first 24 hours. TABLE 17 shows this relationship.

There were no statistically significant differences between treatment groups in the distribution of RDS according to severity of disease (TABLE 18).

TABLE 17. Definition of RDS based on MAP and FiO2.

Definition	Severe*	Moderate	Mild	None**
MAP	≥12	≥ 8 ≤ 12	–	–
FiO2 at 24 hrs. of age	≥ 0.70	≥ 0.40 ≤0.70	≥ 0.30	–

*RDS death within 24 hrs. is also considered severe RDS
**Not mild, or moderate or severe.

TABLE 18. Severity and Occurrence of RDS - Number (Percentage) of Patients - ITT and TBW Populations

Rating of Severity	ITT Population			TBW Population (700-1100 g)		
	Infasurf (N=62)	Exosurf (N=183)	Distributional p-Value*	Infasurf (N=36)	Exosurf (N=97)	Distributional p-Value*
Severe	5 (8.1)	9 (4.9)	0.32	2 (5.6)	4 (4.1)	0.66
Moderate	15 (24.2)	61 (33.3)		8 (22.2)	29 (29.9)	
Mild	42 (67.7)	113 (61.8)		26 (72.2)	64 (66.0)	
None	344 (84.7)	206 (53.0)		197 (84.5)	124 (56.1)	

*p value based on comparison of severe, moderate and mild outcomes only.

(4) Incidence of RDS-related Air Leaks

The incidence of RDS-related air leaks was analyzed based upon chest radiograph readings made at the individual study sites and also based upon chest radiographs read by the central Radiology Reading Committee (RRC).

Total air leaks, by the study sites and by the central RRC, were significantly lower in Infasurf-treated patients than in Exosurf-treated patients, in the ITT population and in the TBW population. Looking specifically at pneumothoraces and PIE at the study sites: there were fewer, statistically significant pneumothoraces in the Infasurf-treated patients in the TBW population than in the Exosurf-treated patients. In the ITT population, Infasurf-treated patients had less pneumothoraces but the difference did not reach statistical significance. At the RRC the incidence of pneumothoraces was similar in both treatment groups. PIE was statistically significantly less frequent in Infasurf-treated patients in the ITT and the TBW populations in both places of determination. Refer to TABLE 19 for incidence of air leaks based upon chest radiographs read at the study sites and by the central RRC (from tables 4.21 and 4.22 vol 1.27).

When the incidence of air leaks was broken down into events that occurred early (≤ 7 days of age) and late (> than 7 days), the results showed that Infasurf -treated patients had statistically significantly less total air leaks and PIE and numerically less pneumothoraces than Exosurf-treated patients at ≤ 7 days of age. The difference was not significant at > 7 days of age.

TABLE 19. Incidence of RDS-Related Air Leaks by place of Chest Radiographs Reading - Number (Percentage) of Patients - ITT and TBW Populations

Efficacy Parameter	Population					
	ITT			TBW		
	Infasurf (N=431)	Exosurf (N=422)	p-value*	Infasurf (N=250)	Exosurf (N=237)	p-value*
Any Air Leak						
Study Sites	42 (10)	79 (19)	0.0002	23 (9)	41 (17)	0.007
RRC*	42 (10)	65 (15)	0.013	22 (9)	34 (14)	0.046
Pneumothorax						
Study Sites	23 (5)	36 (9)	0.067	11 (4)	22 (9)	0.033
RRC*	23 (5)	30 (7)	0.290	11 (4)	18 (8)	0.130
P I E						
Study Sites	23 (5)	58 (14)	0.0001	15 (6)	29 (12)	0.015
RRC*	23 (5)	52 (12)	0.0004	15 (6)	26 (11)	0.040

*Radiology Reading Committee
*Fisher's two-tailed test

Reviewer's note: A major area of discrepancy in CXR readings between the study sites and the RRC was the reading of pulmonary air leaks. These discrepancies, for the most part, did not change the final result in the incidence of each of the variables, except in regard to pneumothoraces. Infasurf-treated patients had statistically significantly less incidence of pneumothoraces than Exosurf-treated patients when their CXR's were read at the study sites, and this difference lost its statistical significance when the CXR's were read at the central RRC.

We wanted to see the incidence of air leaks in the subgroups outside the target birth weight. As expected, there was a higher incidence of total air leaks in infants weighing < 700 g than in those weighing > 1100 g. There was a statistical significance favoring Infasurf-treated infants when analyzing total incidence of air leaks and PIE's at ≤7 days, as seen within the ITT and the TBW population. TABLE 20 shows the incidence of total air leaks, PIE and Pneumothoraces in the infants weighing <700 g. and >1100 g., analyzed by age and place of assignment.

TABLE 20. Incidence of RDS-Related Air Leaks Based Upon Chest Radiographs Read at Each Study Site and the RRC- Number (Percentage) of Patients - Patients outside TBW

Efficacy Parameter	Population					
	<700 g			>1100 g		
	Infasurf (N=98)	Exosurf (N=97)	P Value	Infasurf (N=83)	Exosurf (N=88)	P Value
ANY AIR LEAK						
≤ 7 days						
Study Sites	11 (11)	24 (25)	0.0093	3 (3.6)	8 (9)	0.21*
RRC*	13 (13)	23 (24)	0.04	3 (3.6)	7 (8)	0.33*
> 7 days						
Study Sites	6 (5)	3 (9)	0.43*	0 (0)	2 (2)	0.5*
RRC*	4 (4)	2 (2)	0.68*	0 (0)	1 (1)	1*
PIE						
≤ 7 days						
Study Sites	4 (4)	20 (20)	0.0008	3 (3)	6 (7)	0.5*
RRC*	6 (6)	20 (20)	0.004	2 (2)	5 (6)	0.45*
> 7 days						
Study Sites	1 (1)	5 (5)	0.12*	0 (0)	2 (2)	0.5*
RRC	0 (0)	1 (1)	0.5*	0 (0)	0 (0)	
PNEUMOTHORAX						
≤ 7 days						
Study Sites	7 (7)	8 (8)	0.8*	1 (1)	3 (3)	0.62*
RRC	7 (7)	7 (7)	1*	1 (1)	2 (2)	1*
> 7 days						
Study Sites	5 (5)	3 (3)	0.72*	0 (0)	1 (1)	1*
RRC	4 (4)	2 (2)	0.68*	0 (0)	1 (1)	1*

*RRC= Radiology reading committee
*Fisher's two-tailed test

(5) **Incidence of Crossover Surfactant Treatment**

Requirements established to be eligible for crossover treatment:

i. **The infant had received a full course (3 treatments) of the randomized surfactant,**

ii. **The a/A PO_2 ratio was ≤ 0.10 on two consecutive arterial blood gases obtained more than 4 hours after the final treatment of randomized surfactant, and**

iii. **The infant was < 72 hours old.**

Twenty-six of 422 infants receiving Exosurf (6.2%) required crossover to Infasurf, four of 431 patients initially receiving Infasurf (0.9%) were crossed over to Exosurf therapy ($p < 0.001$). TABLE 21 shows the incidence of crossover within the ITT population.

TABLE 21. Incidence of Crossover - Number (Percentage) of Patients - ITT Population

	Infasurf (N=431)	Exosurf (N=422)	p-Value
Crossover Patients	4 (0.9)	26 (6.2)	< 0.001

Reviewer's note: We reviewed the 30 patients who received crossover treatment, (4 infants initially treated with Infasurf and 26 treated with Exosurf) to see if they all met the criteria for crossover. Sixteen of the infants were not eligible to crossover because they either did not receive the initial 3 doses of prophylactic treatment (n=6), or the two calculated a/A P02 ratios were not ≤ 0.10 before the crossover (n=9) or the age was > 72 hours (n=1) at the time of the crossover. Three of the 16 infants were initially Infasurf-treated, and 13 were Exosurf-treated. TABLE 22 presents the distribution of those patients that did not meet the criteria for crossing over surfactant treatment according to birth weight group and initial treatment received. TABLE 23 shows the incidence of patients who met the criteria for crossover treatment between the treatment groups. There was a statistically significant difference in favor of Infasurf in the incidence of crossover after the review of the individual data listings.

TABLE 22. Patients who did not qualify for crossover treatment, per birth weight. - Number of patients.

Birth Weight group	Infasurf	Exosurf	p-Value*
TBW	2	7	0.145
<700 g	1	5	0.19
>1100 g	0	1	1.0

*Fisher's two-tailed test

Of the 14 infants who were eligible to crossover treatment, 1 was an Infasurf-treated, and 13 were Exosurf-treated patients. TABLE 23 shows the modified incidence of crossovers within the ITT population and the birth weight subsets.

TABLE 23. Modified Incidence of Crossovers (qualifying established criteria) by Birth weight. Number (Percentage) of patients .

Birth weight groups	INFASURF (N=431)	EXOSURF (N=422)	p-Value*
ITT	1 (0.2)	13 (3)	<0.0001
TBW	0 (0)	5 (1.2)	0.052
< 700 g	1 (0.2)	5 (1.2)	0.195
> 1100 g	0 (0)	3 (0.7)	0.24

*Fisher's two-tailed test

TABLE 24 shows a listing of the characteristics (BW group, doses of surfactant received, calculated a/A P02's prior to the crossover dose, and the age of the infant at the time the crossover dose was given) of every infant who received crossover treatment without meeting the pre-established criteria for crossover .

TABLE 24. Characteristics of patients not meeting criteria for crossover surfactant treatment

ID	Treatment	Birth weight group	# doses	First a/A P02	Second a/A P02	AGE
1101152	Infasurf	< 700 g	3	0.34	0.32	44
1101079	Infasurf	700-1100 g	1	0.03	0.05	10
1101221	Infasurf	700-1100 g	3	0.11	0.04	47
1101014	Exosurf	< 700 g	3	0.23	0.13	38
1101151	Exosurf	< 700 g	3	0.14	0.11	28
1112107	Exosurf	< 700 g	3	0.18	0.2	34
1105030	Exosurf	< 700 g	3	0.08	0.1	108
1101146	Exosurf	< 700 g	3	0.02	0.14	44
1101067	Exosurf	> 1100 g	1	0.02	0.02	4
1101187	Exosurf	700-1100 g	2	0.04	0.03	12
1101170	Exosurf	700-1100 g	3	0.09	0.11	32
01228	Exosurf	700-1100 g	3	0.11	0.1	40
1104022	Exosurf	700-1100 g	2	0.06	0.05	12
1101082	Exosurf	700-1100 g	3	0.11	0.12	36
1110012	Exosurf	700-1100 g	2	0.05	0.05	6
1101019	Exosurf	700-1100 g	2	0.02	0.02	13

(6) Incidence of Acute Pulmonary Hemorrhage

The incidence of acute pulmonary hemorrhage was calculated for the ITT and for the TBW populations. No significant difference in the incidence of acute pulmonary hemorrhage between treatment groups was seen in either the ITT or TBW populations. TABLE 25 present the incidence of acute pulmonary hemorrhage.

TABLE 25. Incidence of Acute Pulmonary Hemorrhage and Pneumonia - Number (Percentage) of Patients - ITT and TBW Populations

Parameter	ITT Population (N=853)			TBW Population (700-1100 g) (N=487)		
	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=250)	Exosurf (N=237)	p-Value
Acute Pulmonary Hemorrhage	41 (9.5)	33 (7.8)	0.37	22 (8.8)	15 (6.3)	0.25

Reviewer's note: There were 74 cases of acute pulmonary hemorrhage, 41 and 33 in Infasurf and Exosurf-treated groups respectively. Sixteen cases were in the < 700 gr. infants in both treatment groups, and 3 cases in Infasurf and 2 cases in Exosurf-treated infants in the >1100 gr. group. There were 17 cases of pulmonary hemorrhage at ≥ than 7 days of age. Nine of seventeen (52.9%) were in the Infasurf group, and 8 (47%) in the Exosurf group. There was no statistically significant difference in the incidence of pulmonary hemorrhage at any time during the study between both treatment groups.

(7) Severity of BPD

The severity of BPD was determined from the type of respiratory support required at 28 days post-birth and 36 weeks PCA. There was no significant difference between treatment groups in the distribution of BPD/chronic lung disease severity as related to the type or amount of oxygen supplementation required at either 28 days or 36 weeks PCA for either the ITT or TBW populations. TABLE 26 shows the distribution of the respiratory support received by treatment group at 28 days, TABLE 27 presents the data at 36 weeks PCA (from tables 4.27 and 4.28 vol 1.27).

TABLE 26. Respiratory Support Requirements at 28 days - Number (Percentage) of Surviving Patients - ITT and TBW Populations -

Parameter	ITT Population [N=732]		TBW Population (700 -1100g) [N=442]	
	Infasurf [N=378]	Exosurf [N=354]	Infasurf [N=234]	Exosurf [N=208]
Ventilated	188(49.7)	178 (50.3)	122 (52.1)	101 (48.6)
CPAP*	3 (8.7)	16 (4.5)	26 (11.1)	13 (6.3)
Hood Oxygen	2 (3.2)	16 (4.5)	10 (4.3)	0 (4.8)
Nasal Cannula Oxygen	56 (14.8)	70 (19.8)	35 (15.0)	48 (23.1)
Room Air	89 (23.5)	74 (20.9)	41 (17.5)	36 (17.3)
Distributional p-Values	p = 0.06		p = 0.13	

* CPAP = Continuous positive airway pressure

TABLE 27. Respiratory Support Requirements at 36 Weeks PCA -Number (Percentage) of Surviving Patients - ITT and TBW Populations

Parameter	ITT Population (N=713)		TBW Population (700 -1100 g) (N=434)	
	Infasurf (N=365)	Exosurf (N=348)	Infasurf (N=229)	Exosurf (N=205)
Ventilated	26 (7.1)	27 (7.8)	14 (6.1)	10 (4.9)
CPAP*	5 (1.4)	8 (2.3)	2 (0.9)	5 (2.4)
Hood Oxygen	13 (3.6)	12 (3.4)	9 (3.9)	8 (3.9)
Nasal Cannula Oxygen	112 (30.7)	102 (29.3)	76 (33.2)	60 (29.3)
Room Air	205 (56.2)	199 (57.2)	125 (54.6)	122 (59.5)
Unknown	4 (1.1)	0 (0.0)	3 (1.3)	0 (0.0)
Distributional p-Values	p = 0.43		p = 0.35	

* CPAP = Continuous positive airway pressure

D. Safety Results

(1) Incidence and Severity of IVH

The incidence and severity of IVH was determined from brain sonograms read by the radiologist at each study site and also read by a central radiologist at the Coordinating Study Center (CSC).

Five hundred twenty three of 733 (71%) who survived 28 days had a head ultrasound between 4 and 8 weeks. Appropriate surveillance to capture all periventricular leukomalacia (PVL), i.e., ultrasounds every 14 days, was not incorporated into the protocol, therefore PVL was "cases identified" and not incidence in the population. Approximately 60% of identified cases of PVL by both evaluation methods came from one site, Children's Hospital of Buffalo, which was only 27% of the study population. The Children's Hospital of Buffalo site has an institutional practice of frequent ultrasound examinations in asymptomatic infants older than 4 weeks.

The identification of patients with both PVL and IVH combined was significantly less for Exosurf-treated patients than for Infasurf-treated patients in both the ITT (p=0.004 sites; p=0.002 CSC) and TBW (p=0.001 sites; p<0.01 CSC) populations. Similar results were seen when patients with IVH, PVL, or both were combined and analyzed for the ITT (p=0.006 sites; p=0.03 CSC) and the TBW (p=0.007 sites; p=0.01 CSC). Within both the ITT and TBW populations, there was no significant difference between treatment groups in the distribution of IVH grades of severity (ITT p=0.44, TBW p=0.34). TABLE 28 presents the number of patients with IVH only, PVL only and with their combinations per treatment group in the ITT and TBW populations as determined at the Study Sites. TABLE 29 presents the incidence as determined at the CSC (from tables 4.35 and 4.37 vol 1.27).

TABLE 28. Incidence of IVH, Incidence of PVL, Incidence of PVL and IVH, Combined Incidence, as Determined at Study Sites - Number (Percentage) of Patients - ITT and TBW Populations

Parameter	ITT Population (N=834)			TBW Population (700-1100 g) (N=482)		
	Infasurf (N=423)	Exosurf (N=411)	p-Value	Infasurf (N=248)	Exosurf (N=234)	p-Value
IVH only[a]	163 (38.5)	147 (35.8)	0.40[1]	96 (38.7)	81 (34.6)	0.29[1]
PVL only[a]	14 (3.3)	19 (4.6)	0.38	10 (4.0)	8 (3.4)	0.81
PVL and IVH[a]	39 (9.2)	17 (4.1)	0.004	27 (10.9)	8 (3.4)	0.001
PVL, IVH, or both[a]	216 (51.1)	183 (44.5)	0.06[1]	133 (53.6)	97 (41.5)	0.007[1]

[a] Denominator is the number of infants with either an IVH or PVL determination
[1] Based on logistic regression model

TABLE 29. Incidence of IVH, Incidence of PVL, and Combined Incidence, as Determined Centrally at the Coordinating Study Center - Number (Percentage) of Patients - ITT and TBW Populations.

Parameter	ITT Population (N=853)			TBW Population (700-1100 g) (N=487)		
	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=250)	Exosurf (N=237)	p-Value
IVH only[a]	144 (33.4)	120 (28.4)	0.11[1]	83 (33.2)	65 (27.4)	0.14[1]
PVL only[a]	5 (1.2)	8 (1.9)	0.42	4 (1.6)	2 (0.8)	0.69
IVH and PVL[a]	23 (5.3)	6 (1.4)	0.002	16 (6.4)	3 (1.3)	<0.01
IVH, PVL, or both[a]	172 (39.9)	134 (31.8)	0.01[1]	103 (41.2)	70 (29.5)	0.0007[1]

[a] Denominator is the number of all infants (amendment of August 17,1995)
[1] Based on logistic regression model

In order to investigate more the role of intracranial hemorrhages, the sponsor compared the number of patients who died or who survived but had PVL and/or severe IVH (patients with poor outcomes), with the number of patients who survived without PVL or severe IVH (patients with positive outcome) for both the ITT and TBW populations. There were no significant differences between treatment groups at the study sites and at the coordinating center. The distribution of patients with poor outcomes, and those with positive outcomes are presented in TABLE 30 (as determined at study sites), and TABLE 31 (as determined by the Coordinating Study Center).

TABLE 30. Poor Acute Outcomes: Patients Who Died or Survived with PVL and/or Severe IVH*, as Determined at Study Sites - Number (Percentage) of Patients - ITT and TBW Populations.

Severe IVH*, PVL, and/or Death	ITT Population (N=853)		TBW Population (700 - 1100 g) (N=487)	
	Infasurf (N=431)	Exosurf (N=422)	Infasurf (N=250)	Exosurf (N=237)
Died, or Survived with PVL and/or Severe IVH	156 (36.2)	136 (32.2)	83 (33.2)	61 (25.7)
Survived without PVL or Severe IVH	275 (63.8)	286 (67.8)	167 (66.8)	176 (74.3)
Distributional p-Value	p = 0.22[1]		p = 0.10[1]	

* Severe IVH is defined as grade III or IV on study site evaluation.
[1] Based on logistic regression model.
Cross Reference: Data Listing 6, 12 and 13 of Case Report Tabulations.

TABLE 31. Poor Acute Outcomes: Patients Who Died or Survived with PVL and/or Severe IVH*, as Determined by the Coordinating Study Center - Number (Percentage) of Patients

Severe IVH*, PVL, and/or Death	ITT Population (N=853)		TBW Population (700 - 1100 g) (N=487)	
	Infasurf (N=431)	Exosurf (N=422)	Infasurf (N=250)	Exosurf (N=237)
Died, or Survived with PVL and/or Severe IVH	130 (30.2)	110 (26.1)	68 (27.2)	48 (20.3)
Survived without PVL or Severe IVH	301 (69.8)	312 (73.9)	182 (72.8)	189 (79.7)
Distributional p-Value	p = 0.18[1]		p = 0.10[1]	

* Severe IVH is defined as grade III or IV on study site evaluation.
[1] Based on logistic regression model.
Cross Reference: Data Listing 6, 12 and 13 of Case Report Tabulations.

A report of an ongoing developmental follow-up of 265 patients (Infasurf n= 135 and Exosurf n=130), from four of the sites that participated in this trial, reported cerebral palsy in 18% of Infasurf patients and 17% of Exosurf patients. IVH grade III - IV and/or PVL were present in 13% and 19% of the Exosurf and Infasurf groups. (p=0.24). Thirty seven per cent of Exosurf and 47% of Infasurf patients (p=0.10) had normal neurodevelopmental examinations. (From Appendix 14, vol 1.29 page 08-1689).

For patients with birth weights < 700 g and >1100 g, there were no significant difference between treatment groups in the incidence of IVH only, the incidence of PVL only, the number (percentage) of patients with both PVL and IVH, and the combined incidence of IVH, PVL, or both. Also, there were no statistically significant treatment group differences in the distribution of IVH severity for both the <700 g and >1100 g birth weight populations.

Reviewer's note: The protocol required a head ultrasound to be taken between 3 and 7 days of life and another at 4 - 8 weeks. If the child died before day 3, the last ultrasound before death was evaluated. All patients were evaluated by either a head ultrasound, autopsy, or a clinical definition of IVH for those patients who died with no autopsy and no head ultrasound. They had their IVH assigned by a panel of blinded physicians who contacted each other over the phone and reviewed the patients' records for the above criteria.
The clinical definition of severe IVH, not provided in the protocol, required:

- CNS signs: seizures, split cranial suture, bulging fontanel, etc.,
- falling hemoglobin or hematocrit, and
- signs of cardiopulmonary instability: hypotension, hypoxemia, etc.

The significance of the increased incidence of all grades of IVH/PVL found in the Infasurf-treated group is not known yet. The relationship of the study drug, the not quite clear subsequent management of these infants post-surfactant treatment, and the natural history of the disease is still yet to be elucidated in the causality of this and other complications of prematurity.

In the analysis of the number of patients who either died or had severe IVH, i.e., grades III (intraventricular hemorrhage with ventricular dilatation) and IV (intraparenchymal hemorrhage), or periventricular leukomalacia, the 95% confidence intervals of the difference between Infasurf and Exosurf are as follows:

ITT	Infasurf	Exosurf	P-value	95% CI Inf-Exo
Prophylaxis	N=431	N=422		
Died, or survived with PVL and/or severe IVH	156 (36.2%)	136 (32.2%)	.22	(-0.024, 0.103) 0.039 ± 0.064

The above data indicate with a 95% confidence that Infasurf could be up to 10% worse and 2.4% better than Exosurf in this endpoint. The question comes to be if that is an acceptable limit. Since no limits in the CI range were determined a priori to establish equivalency, it is difficult, if not inappropriate, to try to interpret this result from a statistical point of view now. The clinical relevance of the increase in the incidence of intracranial hemorrhages found in the Infasurf-treated group should be measured against other clinically important parameters found to be improved in the Infasurf-treated group, e.g., incidence of RDS, and RDS and respiratory mortality. Further internal discussions are warranted for the proper incorporation of the data into the labeling. Future studies might be needed to confirm the findings.

(2) Complications of Prematurity

The incidence of these complications of prematurity are shown in TABLE 32 for both the ITT and TBW populations. For all complications evaluated, the between treatment group comparisons show the incidences to be similar in the Infasurf-treated and Exosurf-treated infants.

TABLE 32. **Complications of Prematurity - Number (Percentage) of Patients - ITT and TBW Populations**

Parameter	ITT Population (N=853)			TBW Population (700-1100 g) (N=487)		
	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=250)	Exosurf (N=237)	p-Value
PHHC	31/409 (7.6)	21/392 (5.4)	0.25	19/244 (7.8)	15/225 (6.7)	0.72
Shunt Rx	8/409 (2.0)	4/392 (1.0)	0.39	7/244 (3.3)	2/225 (0.9)	0.18
PDA	223 (51.7)	233 (55.2)	0.34	145 (58.0)	136 (57.4)	0.93
Indocin Rx	151 (35.0)	157 (37.2)	0.52	101 (40.4)	90 (38.0)	0.64
Ligation Rx	65 (15.1)	59 (14.0)	0.70	35 (14.0)	34 (14.3)	1.00
Apnea	316 (73.3)	304 (72.0)	0.70	197 (78.8)	185 (78.1)	0.91
ROP	219/347 (63.1)	231/345 (67.0)	0.30	150/224 (67.0)	147/209 (70.3)	0.47
Cryotherapy Rx	35/347 (10.1)	25/345 (7.2)	0.23	23/224 (10.3)	13/209 (6.2)	0.12
NEC	36 (8.4)	25 (5.9)	0.19	19 (7.6)	16 (6.8)	0.73
Sepsis	136 (31.6)	121 (28.7)	0.37	76 (30.4)	76 (32.1)	0.70

Abbreviations Used
ROP - Retinopathy of prematurity
PHHC - Posthemorrhagic hydrocephalus
NEC - Necrotizing enterocolitis
PDA - Patent ductus arteriosus

Reviewer's note. In a subset analysis, of patients <700 g., Infasurf patients had statistically significantly more incidence of PHHC ($p \leq 0.05$) and sepsis ($p \leq 0.01$) than Exosurf-treated patients. In the subset >1100 g., the Infasurf group had statistically significantly less PDA treated with Indocin than the Exosurf group.

(3) Adverse Events

Adverse events were recorded as bradycardia, airway obstruction, reflux, cyanosis, reintubation, and manual ventilation, when associated to the administration of the surfactants. Between-treatment group comparisons show that more adverse events were associated with administration of Infasurf than Exosurf. Among patients in the ITT population, 86% of Infasurf-treated patients (370 of 431) and 79% of Exosurf-treated patients (332 of 422) experienced at least one adverse event over the course of treatment.

Within the TBW population, 91% of Infasurf-treated patients (227 of 250) and 82% of Exosurf-treated patients (194 of 237) experienced at least one adverse event. Cyanosis was the most frequently reported adverse event among both treatment groups in both the ITT (74% - Infasurf, 62% - Exosurf) and TBW (79% - Infasurf, 63% - Exosurf) populations. Bradycardia, airway obstruction and requirement for manual ventilation were reported for one and one half to nearly twice as many Infasurf-treated patients as Exosurf-treated patients. The adverse events were considered of a transient character. TABLE 33 presents the incidence of adverse events reported over the course of treatment for patients in both treatment groups and populations.

TABLE 33. Total Adverse Events - Number (Percentage) of Patients - ITT and TBW Populations

Parameter	ITT Population (N=853)			TBW Population (700-1100 g) (N=487)		
	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=250)	Exosurf (N=237)	p-Value
Bradycardia	205 (47.6)	125 (29.6)	<0.001	127 (50.8)	81 (34.2)	<0.001
Airway Obstruction	240 (55.7)	150 (35.6)	<0.001	154 (61.6)	87 (36.7)	<0.001
Reflux	88 (20.4)	108 (25.6)	0.07	54 (21.6)	67 (28.3)	0.09
Cyanosis	320 (74.3)	263 (62.3)	<0.001	197 (78.8)	149 (62.9)	<0.001
Reintubation	12 (2.8)	2 (0.5)	0.01	8 (3.2)	0 (0.0)	0.008
Manual Ventilation	103 (23.9)	53 (12.6)	<0.001	65 (26.0)	31 (13.1)	<0.001
Any	370 (85.9)	332 (78.7)	0.007	227 (90.8)	194 (81.9)	0.005

Reviewer's note: The sponsor explained the increased incidence of adverse events during the administration of Infasurf by analyzing the events according to the order of the individual treatments (from TABLES 4.49-4.51 of the submission). Adverse events recorded during the first treatment were similar in frequency for both treatment groups within the ITT and TBW populations with two exceptions: in the ITT population, Exosurf-treated patients had statistically significantly more reflux than Infasurf patients ($p=0.02$); and in the TBW population, Infasurf-treated patients had statistically significantly more airway obstruction than Exosurf-treated patients.

During the repeat doses (after doses 2 and 3), significant differences were seen between the treatment groups in favor of Exosurf. The sponsor claimed that the patients who presented cyanosis and bradycardia were requiring statistically significantly lower FiO2 than the infants who did not have adverse events. This was seen in both treatment groups. More Infasurf-treated infants were on lower FiO2 than Exosurf-treated infants at the time of the repeat dosing. The adverse events reported with Infasurf are claimed to be related to the effectiveness of the surfactant. The effectiveness of Infasurf led to a lower FiO_2, offering less protection against airway obstructions, manual ventilation, cyanosis and bradycardia during subsequent treatments. TABLE 34 shows the incidence of adverse events during the first dosing, TABLES 35 and 36 show the incidence of adverse events during the second and third dosing administrations respectively.

The sponsor post hoc analysis, attempted to explain this phenomenon for various variables like FiO2, MAP etc. to demonstrate an association between some ventilatory variables and the occurrence of the adverse events. The model fit is
FiO2 = Treatment + Bradycardia + Treatment x Bradycardia

The statistical model used by the sponsor failed to demonstrate such relation consistently in the trial. In addition, the validity of the model is questionable since bradycardia, cyanosis, and airway obstruction are outcomes of the study and not predictors.

Furthermore, one can argue that if a patient was improving, requiring less FiO2 for the management of his/her condition to maintain acceptable PaO2 levels, that patient should have been able to tolerate better the administration of the surfactant. Besides, the levels of FiO2 supplementation can not explain the increase incidence of airway obstruction and/or manual ventilation. Bradycardia and cyanosis could be better explained associated with the increased incidence of airway obstruction and the resulting increase in the need of reintubation and/or manual ventilation. These adverse events associated with the administration of Infasurf are consistent with those found in other Infasurf trials and should be addressed properly in the labeling.

TABLE 34. Adverse Events - Treatment 1 - Number (Percentage) of Patients Reporting Adverse Events - ITT and TBW Populations

Variable	Infasurf (N=431)	Exosurf (N=422)	p-Value	Infasurf (N=250)	Exosurf (N=237)	p-Value
Bradycardia	9 (2.1)	6 (1.4)	0.60	3 (1.2)	1 (0.4)	0.62
Airway Obstruction	21 (4.9)	10 (2.4)	0.07	15 (6.0)	4 (1.7)	0.02
Reflux	46 (10.7)	69 (16.4)	0.02	26 (10.4)	36 (15.2)	0.14
Cyanosis	29 (6.7)	23 (5.5)	0.48	19 (7.6)	11 (4.6)	0.19
Reintubation	7 (1.6)	2 (0.5)	0.18	4 (1.6)	0 (0.0)	0.12
Manual Ventilation	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Any	91 (21.1)	89 (21.1)	1.00	54 (21.6)	45 (19.0)	0.50

Cross Reference: Data Listing 14 of Case Report Tabulations (NDA Section XI)

TABLE 35. Adverse Events - Treatment 2 - Number (Percentage) of Patients Reporting Adverse Events - ITT and TBW Populations

Parameter	ITT Population (N=745)			TBW Population (700-1100 g) (N=440)		
	Infasurf (N=373)	Exosurf (N=372)	p-Value	Infasurf (N=226)	Exosurf (N=214)	p-Value
Bradycardia	137 (36.8)	69 (18.6)	<0.001	90 (39.8)	44 (20.6)	<0.001
Airway Obstruction	157 (42.2)	94 (25.3)	<0.001	97 (42.9)	58 (27.1)	<0.001
Reflux	36 (9.7)	43 (11.6)	0.48	24 (10.6)	31 (14.5)	0.25
Cyanosis	246 (66.1)	181(48.7)	<0.001	155 (68.6)	103 (48.1)	<0.001
Reintubation	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Manual Ventilation	66 (17.7)	25 (6.7)	<0.001	40 (17.7)	14 (6.5)	<0.001
Any	296 (79.6)	238(64.0)	<0.001	186 (82.3)	139 (65.0)	<0.001

Cross Reference: Data Listing 14 of Case Report Tabulations (NDA Section XI)

TABLE 36. Adverse Events - Treatment 3 - Number (Percentage) of Patients Reporting Adverse Events - ITT and TBW Populations

Parameter	ITT Population (N=659)			TBW Population (N=393)		
	Infasurf (N=330)	Exosurf (N=329)	p-Value	Infasurf (N=202)	Exosurf (N=191)	p-Value
Bradycardia	138 (41.7)	80 (24.3)	<0.001	84 (41.6)	51 (26.7)	0.002
Airway Obstruction	159 (48.0)	79 (24.0)	<0.001	102 (50.5)	40 (20.9)	<0.001
Reflux	28 (8.5)	16 (4.9)	0.09	19 (9.4)	13 (6.8)	0.36
Cyanosis	244 (73.7)	180(54.7)	<0.001	146 (72.3)	105 (55.0)	<0.001
Reintubation	5 (1.5)	0(0.0)	0.06	4 (2.0)	0 (0.0)	0.12
Manual Ventilation	66 (19.9)	31 (9.4)	<0.001	42 (20.8)	19 (10.0)	0.003
Any	286 (86.4)	214(65.1)	<0.001	176 (87.1)	127 (66.5)	<0.001

Cross Reference: Data Listing 14 of Case Report Tabulations (NDA Section XI)

E. Additional Comments

When reviewing the data, we noticed that 42 patients in the ITT population received "non-protocol (NP) doses of surfactant", i.e., doses of surfactant given in violation of the protocol (either before the next dose was due, or after the 48 hrs of age). When asked, the sponsor explained the nature of these doses in an amendment to the NDA on September 1, 1995. The sponsor stated that the site investigators decided to violate the protocol when, in their opinion, this was in the best interest of the patient. From the above cited letter we learned that of the 42 patients that received "NP surfactant doses", 16 patients were in the Infasurf group and 26 patients were in the Exosurf group. Eight of the 16 (50%) Infasurf patients, and 24 of the 26 (92%) Exosurf patients received other surfactant than that to which the patient was randomized. The sponsor included all these patients in all the efficacy and safety analysis in their original randomized treatment group because " no prospective provision had been made to exclude patients for NP doses." See the tabulated data below and TABLE 37 for a distribution of the patients who received a NP surfactant dose, as submitted by the sponsor.

	Infasurf	Exosurf
Total receiving NP dose	16/431(4%)	26/422(6%)
NP drug was the randomized study drug	8/16	2/26
NP drug was the other study drug	2/16	21/26
NP drug was Survanta	6/16	3/26

TABLE 37. Non-Protocol surfactant administered by randomized treatment group. Number /total (percentage) of patients. ITT population.

Rx'ed Surfactant	Non-Protocol surfactant administered		
	Infasurf	Exosurf	Survanta
Infasurf	8/16 (50)	2/16 (12.5)	6/16 (37.5)
Exosurf	21/26 (80.7)	2/26 (7.7)	3/26 (11.5)

It is not clear how the NP doses where indicated. The blinding status of the trial could be questioned. Why so many more infants randomized to Exosurf received Infasurf as the NP surfactant i.e., 21/26 or 81%. The sponsor explained that for personal preference, the investigators ordered Infasurf for those patients who were doing poorly without meeting criteria for retreatment, without unblinding the initial randomized surfactant . Since the outcome of this NP doses were analyzed for the original randomized group, the beneficial effect of these NP doses could be, if any, running against the sponsor's surfactant. The introduction of a third surfactant (Survanta) in 9/42 cases (21.4%), presents a confounding variable in the analysis of the data.

To explore the effect that NP surfactant doses may have had in the results, we first scanned every patient individually to identify their birth weight distribution, and then we identified their particular outcomes related to the main efficacy and safety variables. TABLE 38 shows that most of the patients who received NP doses were <1100 grams of birth weight. Fourteen of the 16 (87.5%) NP doses, were given to the < 1100 gram population in the Infasurf group and 24/26 (92%) of the cases in the Exosurf group.

TABLE 38. Non-Protocol surfactant doses by birth weight. Number (percentage) of patients. ITT population

Rz'ed Treatment	< 700 g	700 - 1100 g	> 1100 g
Infasurf (N=16)	5 (31)	9 (56)	2 (12.5)
Exosurf (N=26)	12 (46)	12 (46)	2 (7.7)

TABLE 39 presents the individual outcomes of the patients that received NP doses of surfactant. In the Infasurf group, 5 of 16 patients (31%) developed RDS, with a total mortality of 2/16 (8%), none of them were RDS related. In the Exosurf group, 15 of 26 infants (58%) developed RDS and there were 13/26 (50%) deaths, 3 of them were considered RDS related. These patients were in more critical conditions, nevertheless, the results in incidence of RDS and total mortality do not indicate a different trend than that found in the analysis of the total population.

TABLE 39. Outcome of patients that received Non-Protocol doses, by randomized surfactant. ITT population

Rz'ed Treatment	NP surfactant Rec'd.	RDS	Avg FiO2 at 24 hrs.	# Deaths RDS/Total	IVH or PVL
Infasurf	Infasurf (n = 8)	4	44%	0/2	3
	Exosurf (n = 2)	0	25%	0/0	1
	Survanta (n = 6)	1	40.5%	0/0	4
Exosurf	Infasurf (n = 21)	11	48.4%	3/10	6
	Exosurf (n = 2)	2	100%	0/2	1
	Survanta (n = 3)	2	46.5%	0/1	0

As a final analysis, we excluded all the patients who received non-protocol surfactant doses from our hypothetical worse case scenario, where we had excluded all patients that met any of the original exclusion criteria and had assigned as with RDS all patients in the Infasurf group that were considered by the sponsor as RDS indeterminate. In this scenario, Infasurf-treated patients again had a statistically significant difference in the incidence of RDS in their favor over the Exosurf-treated patients.

TABLE 40. Modified RDS analysis by birth weight, excluding patients who met any of the exclusion criteria or violated the protocol.

Treatment	ITT	TBW	< 700 g	>1100 g
Infasurf	53/304 (17%)	31/173 (18%)	18/66 (27%)	4/65 (6%)
Exosurf	132/281 (47%)	74/166 (44.5%)	42/64 (66%)	16/51 (31%)
p-value	< 0.0001	< 0.0001	0.0001	0.001

10. Summary

In this trial, 853 infants received test drug treatment, 431 infants received Infasurf and 422 infants received Exosurf.

Both groups were similar in demographic and obstetric characteristics.

Results That Supported Approval

Infasurf was statistically significantly better than Exosurf in decreasing the incidence of RDS, even in our most conservative approach (p<0.001), and the incidence of deaths due to RDS (p=0.019 after the individual review of CRF's). Fewer respiratory deaths occurred in Infasurf patients than in Exosurf patients within both the ITT (p=0.01 committee; p=0.03 sites) and TBW (p=0.05 committee; p=0.02 sites) populations. Fewer Infasurf patients developed any air leak within the ITT (p=0.13 committee; p<0.01 sites) and TBW (p=0.007 committee; p=0.046 sites) groups. PIE was also statistically significantly decreased in the Infasurf group, regardless of place of determination in the ITT and the TBW populations.

Results That Did not Support Approval

Infasurf had statistically significantly more incidence of IVH and PVL combined at the study sites (p=0.004) and at the coordinating study center (p=0.002) than Exosurf. Infasurf patients also had statistically significantly more adverse events during the administration of the surfactant: bradycardia (p<0.001), airway obstruction (p<0.001), cyanosis (p<0.001), reintubation (p=0.01), and manual ventilation (p<0.001).

Other Results

Severity of RDS and BPD, incidence of pulmonary hemorrhages, and the most common complications of prematurity (ROP, PDA, NEC, PHHC, sepsis) were similar in both groups. The assessments of survival without severe IVH or PVL and of patients with poor outcome (patients who died or developed severe IVH or PVL) was comparable in both treatment groups.

11. Discussion And Conclusions

Based on the results of this trial, Infasurf demonstrated enough evidence of efficacy in the prophylaxis of RDS by showing superiority over Exosurf in clinically important parameters such as the incidence of RDS, death due to RDS, respiratory deaths, and incidence of air leaks.

Safety wise, the most remarkable finding is that Infasurf showed a statistically significant increase in the incidence of IVH and PVL combined, as determined by either the study site investigators or the central reader. This increase in intracranial hemorrhages was also found in the treatment trial. Because of the ambiguity in the etiology of intracranial bleeding and the wide spectrum of types and degrees of bleeding that it involves, which have different impact in the neurodevelopment of the individual, it becomes difficult to establish the safety of Infasurf based on the information available on this parameter alone. Some points are worthy to discuss here: The IVH grades I and II are of unclear clinical significance and ordinarily are not associated with developmental impairment. It is appropriate to compare the benefit of increased survival vs. the risk of developing severe IVH or PVL, considered to have poor developmental prognosis, between the Infasurf and the Exosurf-treated groups. In the post-hoc analysis of poor outcomes (number of patients who died or survived with PVL or severe IVH) presented by the sponsor, there was a 4% difference, not statistically significant, in favor of Exosurf. The 95% confidence interval of the difference between Infasurf and Exosurf for this study is (-0.024, 0.103). One could state with 95% confidence that Infasurf treatment could be as much as 10.3% worse and as much as 2.4% better than the Exosurf treatment in this endpoint. As stated before, there is not information of the implication of this finding in the overall safety of Infasurf, and further internal discussions are warranted to discuss this issue. The labeling should properly reflect the outcome of these discussions.

Infasurf also presented statistically significantly more adverse events (bradycardia, cyanosis, airway obstruction and reintubations) during its administration than Exosurf. These events were considered transient and not severe and information on their monitoring should be incorporated into the labeling.

There were no other statistically significant differences observed in the safety profiles of Infasurf and Exosurf.

CONTROLLED, PIVOTAL STUDIES. SURFACTANT COMPARISON TRIAL (SCT) INFASURF VS. EXOSURF.

II. TREATMENT TRIAL (SCT-T)

1. **Trial Officers and Investigational Centers:**

   A. **Principal Investigator:** Mark L. Hudak, M.D.
   State University at Buffalo, NY

   B. **Sponsor:** Edmund A. Egan, M.D.
   President & Medical Director,
   ONY, Inc.

   C. **Participating Centers:** Treatment trial: 22 centers

2. **Objective**
   To determine the differences in efficacy between Infasurf and Exosurf in the treatment of Respiratory Distress Syndrome in Premature infants. The secondary objective was to assess the safety profile of Infasurf compared to that of Exosurf.

3. **Study Design**
   Phase III, multicenter, randomized, masked, active control, parallel study.

4. **Inclusion Criteria.**
   A. Established RDS (clinical criteria and consistent CXR findings),
   B. Requires mechanically assisted ventilation,
   C. a/A P02 < 0.22,
   D. Less than 72 hours of age.
   E. At the time of treatment, the infant was considered to be stable by the following criteria:
   - Normal heart rate and blood pressure,
   - Normal glucose,
   - Extra-pulmonary air leaks (if identified before treatment) were evacuated and/or controlled,
   - Seizures (if present before treatment) were controlled on anticonvulsant therapy.

Reviewer's note: There was no limitation for gestational age or birth weight in the inclusion criteria.

5. **Exclusion Criteria**
   A. Age > 72 hours,
   B. Previous exposure to surfactant therapy,
   C. Severe congenital anomalies.

6. **Blinding and Administration of surfactant**
   A. Infants were randomized in the order in which they were enrolled into the study. The assigned surfactant was prepared in a private area, and administered by a nurse who would not participate directly in the primary care of the infant for at least 5 days. This nurse was appointed at the beginning of every shift. She was assisted by 2 experienced neonatal resuscitators in the positioning and monitoring of the infant during the administration of the surfactant.

   B. Exosurf and Infasurf doses were administered the same way. Two doses were given 12 hours apart after the diagnosis of RDS. The dose was instilled into the proximal end of the ETT over several minutes during the inspiratory phase of the ventilatory cycle.

   C. Dosages. For Infasurf: 3 ml/kg body weight
   For Exosurf: 5 ml/kg body weight.

Reviewer's note: Infasurf formulation had 35 mg of phospholipids/ml.

   D. Crossover.
   Infants < 96 hours of age, who completed a full course of the randomized surfactant treatment and persisted with a/A PO2 < 0.10 on two consecutive ABG's, obtained more than 4 hours after the final treatment of randomized surfactant, received crossover treatment. This treatment followed the procedure for rescue treatment, two total doses 12 hours apart, each dose divided in two equal aliquots.

7. **Endpoints**
   A. Primary Efficacy Measure:
   - Incidence of RDS-related air leaks,
   - Severity of RDS over the first 24 hours*,
   - Incidence of BPD at 28 days,
   - Mortality secondary to RDS*,

B. Secondary Efficacy and Safety Measures:

- **Total respiratory mortality [early (<7 days) and late (>7 days)],**
- **Total neonatal mortality (at 7 and 28 days),**
- **Incidence of crossover surfactant treatment,**
- **Incidence of acute pulmonary hemorrhage,**
- **Severity of BPD*,**
- **Oxygenation and ventilatory support requirements, and**
- **Total mortality at time of discharge from the hospital*.**

C. Other Safety Endpoints:

- **Incidence and severity of IVH,**
- **Complications of prematurity,**
- **Adverse events.**

Reviewer's note: The above endpoints with an (*) were included in the study report but they were not incorporated in the original protocol, nor were they included in its amendment of April 2, 1991. Only the incidence of air leaks was specified as the primary endpoint in the protocol.

8. Statistical Analysis

A. Sample size. Exosurf treatment is assumed to have resulted in a 34% incidence of total pulmonary air leak. Four hundred analyzable patients (200 in each treatment group) weighing 700-1350 grams birth weight were needed to be able to reduce this by 37%, with a two sided $\alpha = 0.05$, with an 80 percent power.

B. Primary Efficacy Variables. Primary efficacy variables were analyzed using a logistic regression model including the factors of treatment, center and treatment by center interaction. Treatment by center interaction was dropped from the model because the interactions were either statistically not significant or the model did not fit. Whenever the model did not fit, the Fisher's exact two-tailed test for a 2x2 contingency table was used. The centers that had 10 or fewer patients within either treatment group, within the target birth weight group, were combined into one center. The CATMOD (categorical data modeling) procedure of SAS was used to fit the logistic regression model.

C. All p-values associated with qualitative variables in this review are obtained from the CATMOD procedure (where the logistic regression model is fit to the data), unless it is indicated otherwise. P-values associated with quantitative variables are obtained from the t-test.

D. Statistical significance was declared if two-sided p-value was ≤ 0.05.

9. Results

A. Demographic Characteristics

(1) Enrollment

As shown in Table 1, a total of 1,133 patients were enrolled and randomized across 22 centers. In the ITT population, 570 (51%) were randomized and treated in the Infasurf group and 556 (49%) in the Exosurf group (the sample size goal was 200 patients per arm). Within the TBW population (700 g to 1350 g BW), 190 (47%) patients were enrolled and treated in the Infasurf group and 213 (53%) patients were in the Exosurf group . Seven patients in the ITT population (4 in the Infasurf and 3 in the Exosurf group) were enrolled and randomized but were never treated. These patients were excluded from all analyses. All of the seven untreated patients were in the >1350 g population.

TABLE 1. Total distribution of patients entered. ITT and TBW Populations

Treatment	ITT Population N= 1133		TBW Population N= 303	
	Infasurf	Exosurf	Infasurf	Exosurf
Total randomized	574	559	190	213
Total Randomized and Treated	570	556	190	213
Total Rz and <u>NOT</u> treated	4	3	0	0
p-Value	0.53		0.56	

Cross Reference: Data Listing 1 of Case Report Tabulations (NDA Section XI)

Reviewer's note: Even though the protocol did not specify a target birth weight (TBW) population as an inclusion criteria, the sponsor proceeded to analyze the data by considering the infants weighing from 700 g to 1350 g as the TBW population. Table 2 shows the distribution of patients by treatment and birth weight.

TABLE 2. Distribution of infants per birth weight.

Population	Not treated (N=7)	Infasurf (N= 570)	Exosurf (N= 556)	Row Summary (N=1126)
< 700 g	0	36 (6.3)	34 (6.1)	70
>1350 g	7	344 (60.4)	309 (55.6)	660
700 - 1350 g	0	190 (33.3)	213 (38.3)	403
Distributional p-value		0.22		

(2) Neonatal Demographics

The following baseline parameters were compared between treatment groups: birth weight, gestational age, sex, race, percentage of multiple births, percentage of inborn infants (those born at individual study sites), respiratory status at time of study entry, and time of entry. Apgar scores at one and five minutes, and cord pH were also compared in between treatment group analyses.

When comparing the two treatment groups in the ITT population, Infasurf-treated patients had statistically significantly larger birth weight (p=0.04) and greater gestational age (p=0.02) than Exosurf-treated patients. Infasurf-treated patients had Apgar scores at 5 minutes statistically significantly higher (p < 0.01) than Exosurf-treated patients in the TBW population.

Table 3 shows the demographic characteristics of both groups.

TABLE 3. Neonatal Demographics - ITT Population

Parameter	Infasurf (ITT N=570) (TBW N=190)	Exosurf (ITT N=556) (TBW N=213)	p-Value
Birth Weight, grams (mean ± Std. Dev.)			
ITT	1648.2 ± 720.8	1563.7 ± 680.0	0.04
TBW	1063.3 ± 183.9	1035.8 ± 182.5	0.13
Gestational Age, weeks (mean ± Std. Dev.)			
ITT	31.0 ± 3.5	30.6 ± 3.3	0.02
TBW	28.4 ± 1.9	28.2 ± 1.9	0.22
Sex (% Male)			
ITT	327/570 (57.4)	347/556 (62.4)	0.09
TBW	102/190 (53.7)	126/213 (59.2)	0.31
Race (%White)			
ITT	401/567 (70.7)	375/552 (67.9)	0.33
TBW	115/188 (61.2)	124/212 (58.5)	0.69
Apgar 1'			
ITT	5.5 ± 2.4 (N=559)	5.3 ± 2.6 (N=542)	0.27
TBW	4.8 ± 2.2	4.6 ± 2.4	0.24
Apgar 5'			
ITT	7.4 ± 1.7 (N=559)	7.2 ± 1.9 (N=543)	0.32
TBW	7.2 ± 1.7	6.7 ± 2.2	<0.01

Cross Reference: Data Listing 1 of Case Report Tabulations (NDA Section XI)

Reviewer's note: When comparing the demographic data of the two treatment arms, a statistically significant difference in favor of the Infasurf-treated group is noted in the ITT population relative to birth weight (1648.2 ± 720.8 vs. 1563.7 ± 680.0, p=0.04) and gestational age (31.0 ± 3.5 vs. 30.6 ± 3.3, p=0.02). Patients that are older and larger may have better prognosis in respiratory outcomes, and so, at first glance, it seems that Infasurf patients had an advantage over their counterparts. However, the clinical relevance of the size of the differences can be questioned, especially in regard to the gestational age, where the difference of the actual numbers is very small. This difference was not seen in the TBW population.

(3) **Obstetrical Demographics**

The following pregnancy-related variables were recorded: prenatal steroids, tocolysis, labor, rupture of membranes > 1 hour, chorioamnionitis, C-section, abruptio placentae, placenta previa, gestational diabetes, insulin-dependent diabetes, preeclampsia, and oligohydramnios > 14 days.

In the ITT population, the only statistically significant difference between treatment groups was seen in the percentage of mothers who had a prolonged (> 1 hour) rupture of membranes before delivery, with 47.8% in the Exosurf group versus 40.6% in the Infasurf group ($p=0.02$).

Reviewers' note: The sponsor claims that the difference in prolonged rupture of membranes before the onset of labor may induce surfactant and lower the incidence of RDS. Since, in this trial, the patients had to have RDS in order to be enrolled in the study, this difference will not make any impact in the results.

B. **Efficacy Results**

(1) **Incidence of RDS-Related Air Leaks**

RDS-related air leaks were defined to be pneumothorax or PIE. The incidence of pneumothorax and PIE were grouped to calculate the incidence of any air leak during this study. It was also noted whether the air leak occurred early (≤ 7 days) or late (> 7 days). Early air leak was considered to be a primary parameter measuring surfactant effectiveness.

The incidence of RDS-related air leaks was analyzed according to assignments made at individual study sites based on routine radiologic interpretation of chest radiographs and also according to assignments made at the central coordinating center based on review of chest radiographs by the RRC. Both radiologic assessments were made under blinded conditions.

In both the ITT and TBW analyses, there were statistically significantly fewer air leaks (either pneumothorax or PIE) among Infasurf-treated infants than Exosurf-treated patients. This is true whether the radiographs were evaluated at the individual study sites or by the RRC.

Data with respect to air leaks from neonates with birth weights outside of the target birth weight range (i.e., birth weights <700 g or >1350 g) were also assessed. There was a tendency for fewer air leaks following Infasurf treatment than Exosurf treatment. For babies weighing more than 1350 g, statistically significant fewer Infasurf-treated patients than Exosurf-treated patients had evidence of PIE. This was true whether radiographs were read at the study site (3.5% - Infasurf versus 9% - Exosurf; p=0.004) or by the RRC (3.8% versus 9%; p=0.01).

Table 4 shows the incidence of air leaks by place of determination in the ITT and TBW population, and Table 5 shows that incidence in the <700 g and > 3500 g groups.

TABLE 4. Air Leaks anytime during the study by place of assignment - Number (Percentage) of Patients.

Parameter	ITT Population (N=1126)			TBW Population (700-1350 g) (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value	Infasurf (N=190)	Exosurf (N=213)	p-Value
Any Air Leak						
• Study site	79 (13.9)	137 (24.6)	<0.001	40 (21.1)	81 (38.0)	<0.001
• RRC	60 (10.5)	120 (21.6)	<0.001	28 (14.7)	71 (33.3)	<0.001
Pneumothorax						
Study site	42 (7.4)	66 (11.9)	0.01	17 (8.9)	34 (16.0)	0.05
RRC	29 (5.1)	57 (10.3)	0.001	12 (6.3)	32 (15.0)	<0.01
PIE						
Study site	49 (8.6) 39	105 (18.9)	<0.001	30 (15.8)	65 (30.5)	<0.001
RRC	(6.8)	94 (16.9)	<0.001	19 (10.0)	56 (26.3)	<0.001

• the 95% Confidence Interval for difference between treatment group percents was 10.7 ± 4.6 (ITT Population) and 16.9 ± 8.7 (TBW Population)

• the 95% Confidence Interval for difference between treatment group percents was 11.1 ± 4.3 (ITT Population) and 18.6 ± 8.1 (TBW Population)

Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

TABLE 5. Air Leaks Occurring Anytime during the Study by place of assignment - Number (Percentage) of Patients - Neonates under 700 g or over 1350 g.

Parameter	Birth Weight Population: < 700 g			Birth Weight Population: > 1350 g		
	Infasurf (N=36)	Exosurf (N=34)	p-Value	Infasurf (N=344)	Exosurf (N=309)	p-Value
Any Air Leak						
Study site	8 (22.2)	14 (41.2)	0.10	31 (9.0)	42 (13.6)	0.06
RRC	8 (22.2)	12 (35.3)	0.11	24 (7.0)	37 (12.0)	0.03
Pneumothorax						
Study site	3 (8.3)	5 (14.7)	0.39	22 (6.4)	27 (8.7)	0.26
RRC	3 (8.3)	4 (11.8)	0.58	14 (4.1)	21 (6.8)	0.12
PIE						
Study site	7 (19.4)	13 (38.2)	0.09	12 (3.5)	27 (8.7)	0.004
RRC	7 (19.4)	11 (32.4)	0.11	13 (3.8)	27 (8.7)	0.01

Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

Reviewer's note: Incidence of air leaks is the most important difference favorable to Infasurf, noted in the primary endpoints in this trial. The difference in the ITT and TBW groups, though with different numbers, showed statistically significant differences in favor of Infasurf in both places of CXR interpretation, i.e., the study sites and the central reader.

It is noteworthy, though, that PIE, which is a radiologic diagnosis with more room for subjective interpretation by different radiologists, presented a higher concordance among site and RRC radiologists than we see in the interpretation of pneumothoraces. In the >1350 gram group, we found that the RRC decreased the incidence of pneumothoraces, in the Infasurf-treated group, by almost one third of those diagnosed in the study sites. In the Exosurf-treated group this diagnosis was reduced by the RRC from 27 cases to 21(8.7 to 6.8%). Even with these changes, the results continued to show a tendency by Infasurf to present less air leaks. The <700 gram group did not show any significant difference between both groups regardless of the place of interpretation. Information of the severity of the air leaks and the clinical relevance of the air leaks in the overall management of the patient was not provided in this submission for this trial. However, the sponsor claimed that any air leak is associated with clinically and statistically higher risk of death. The sponsor presented data in the submission of November 6, 1995 where they compared mortality with air leaks. From the 2 pivotal studies with Exosurf and the 2 studies with Survanta (N= 3,098 patients) they showed a 40% mortality in patients who had any type of air leaks 204/505 vs. a 10% mortality in those who did not have air leaks 262/2593 chi-square 303 p-value <0.000001. Each study individually also presented a statistically significant improvement in mortality for patients who did not have any air leaks over those did have air leaks.

(2) Severity of RDS

The severity of RDS was calculated using an algorithm that utilized both the FiO2 and the mean airway pressure (MAP) over the first 24 hours. Table 6 shows this relationship.

Table 6. Definition of RDS based on MAP and FIO2.

Definition	Severe*	Moderate	Mild	None**
MAP	>12	≥ 8 ≤ 12	–	–
FIO2 at 24 hrs. of age	> 0.70	≥ 0.40 ≤0.70	≥ 0.30	–

*RDS death within 24 hrs. is also considered severe RDS
**Not mild, or moderate or severe.
MAP = Mean Airway Pressure
FIO_2 = Inspiratory Oxygen Fraction

Comparisons between treatment groups were made of the severity of RDS prior to the first surfactant treatment. There was no difference in the severity of RDS between the Infasurf-treated and Exosurf-treated infants either in the ITT population (p=0.85) or TBW population (p=0.72). In both treatment groups and in both populations evaluated, more than two thirds of the patients had moderate to severe RDS immediately prior to first surfactant administration. TABLE 7 presents the severity of RDS prior to surfactant treatment for all patients in the ITT population and for neonates in the TBW population.

Table 7. Severity of RDS Prior to Surfactant Instillation - Number (Percentage) of Patients - ITT and TBW Populations.

Rating of Severity	ITT Population (N=1126)			TBW Population (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value[1] (Distributional)	Infasurf (N=190)	Exosurf (N=213)	p-Value[1] (Distributional)
Severe	72 (12.7)	75 (13.7)	0.85	26 (13.7)	35 (16.8)	0.72
Moderate	319 (56.5)	301 (55.1)		110 (57.9)	115 (55.0)	
Mild	174 (30.8)	169 (31.0)		54 (28.4)	58 (27.8)	
None	0 (0.0)	1 (0.2)		0 (0.0)	1 (0.5)	
Unknown	5	10		0	4	

[1] Fisher's exact test excluding category Unknown.
Cross Reference: Data Listing 5 of Case Report Tabulations (NDA Section XI)

Reviewer's Note: Severity of RDS is one of the primary endpoints, nevertheless, no analysis was made of progression of severity of RDS post surfactant treatment as a measure of efficacy. The above analysis is a mere comparison of the two groups before treatment, that same analysis should have been done after 24 hours of therapy with the surfactants. The sponsor explained that because of the algorithm used to determined the severity of RDS in the prophylaxis study, which provided that the assessment be done at around 24 hours of age, such determinations could not be done in this trial (many patients were not yet enrolled by the time they were 24 hours of age). No statement on progression of the disease progress can be derived from the data available in this trial.

(3) Incidence of BPD

The incidence of BPD was defined by oxygen dependence and the Edwards-Toce X-ray Score ≥ 4 at 28 days. Infants who survived to 28 days without occurrence of BPD were defined to have intact cardiopulmonary (CP) survival.

EDWARDS-TOCE X-RAY SCORE
The five parameters below were scored as normal (0), mildly or moderately abnormal (1), or markedly abnormal (2). The five parameters evaluated are:

- **cardiovascular abnormalities,**
- **hyperexpansion,**
- **emphysema,**
- **fibrosis or interstitial abnormalities, and**
- **overall subjective appearance of radiograph.**

There were no statistically significant differences between treatment groups either for the ITT , the TBW and the >1350 g population. In the <700 g population there was a statistically significant difference in the incidence of BPD in favor of the Infasurf treated group . Table 8 show the incidence of CP survival and BPD in the ITT and the TBW population. Table 9 shows these incidence in the <700 g and >1350 g BW population.

TABLE 8. Incidence of BPD - ITT and TBW populations. Number/total (percentage) of patients.

Parameter	ITT population (N=1126)			TBW population (700 - 1350 g) (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	p-value	Infasurf (N=190)	Exosurf (N=213	p-value
Intact CP survival[a]	498/570 (87.4%)	468/556 (84.2%)	0.15	148/190 (77.9%)	164/213 (77.0%)	0.91
BPD[ab]	25/523 (4.8%)	30/496 (6.0%)	0.41	20/168 (11.9%)	16/180 (8.9%)	0.38

[a]Defined as infants who survived and do not have BPD at 28 days.
[b]Denominators indicate survivors with data.
[a]Receiving O_2 at 28 days and positive chest radiograph

TABLE 9. Incidence of BPD -Number (Percentage) of Patients - Patients under 700 g and over 1350 g

Parameter	Birth Weight Population: < 700 g (N=70)			Birth Weight Population: > 1350 g (N=653)		
	Infasurf (N=36)	Exosurf (N=34)	p-Value	Infasurf (N=344)	Exosurf (N=309)	p-Value
Intact CP survival[a]	5/36 (13.9)	2/34 (5.9)	0.43	297/344 (86.3)	263/309 (85.1)	0.66
BPD[a,b]	3/19 (15.8)	11/21 (52.4)	0.01	2/336 (0.6)	3/295 (1.0)	0.56

[a]Defined as infants who do not have BPD and survive to 28 days
[b]Denominators indicate survivors with data
[a]Receiving O_2 at 28 days and positive chest radiograph

Reviewer's note: In Tables 8 and 9, the sponsor assessed incidence of BPD from the total of patients who survived to 28 days. In order to assess the incidence of BPD without being influenced by the survival rate, analogous to our analysis of the same endpoint in the Prophylaxis trial (even though in the treatment trial there was not a statistically significant difference in the survival rates between both treatment groups over all) we wanted to look at the incidence of BPD using as the denominator the total of patients initially treated in each arm. Table 10 shows the modified incidence of BPD. Again, there was a statistically significant difference in the incidence of BPD in the <700 g population only in favor of Infasurf.

TABLE 10. Modified incidence of BPD by Birth Weight per treatment group. Number/total (percentage) patients treated.

Treatment	ITT	TBW	<700 g	>1350 g
Infasurf	25/570(4)	20/190(10.5)	3/36(8)	2/344 (0.5)
Exosurf	30/556(5)	16/213(7.5)	11/34(32)	3/309(0.9)
p-value*	0.49	0.30	0.017	0.672

* Fisher's two-tailed test

(4) Mortality Secondary to RDS

Mortality secondary to RDS was defined as death primarily due to RDS and its complications, that occurred at or before 14 days and was not associated with culture positive sepsis/pneumonia, or with pulmonary hypoplasia. Data were analyzed according to assignments made at individual study sites and also according to assignment made at the central coordinating committee (CCC) based on the interpretation of the CxR made by the Radiology reading center (RRC).

There were no statistically significant differences between treatment groups in the incidence of death due to RDS in any of the birth weight subsets or in the ITT. This was true at the individual study sites and at the central committee level. See TABLE 11 for mortality secondary to RDS by place of determination in the ITT and TBW population.

TABLE 11. Mortality secondary to RDS by place of determination. Number (Percentage) of patients. ITT and TBW groups

RDS Death	ITT Population (N=1126)			TBW Population (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	p-value	Infasurf (N=190)	Exosurf (N=213)	p-value
Study sites	20 (3.5)	28 (5.0)	0.21	12 (6.3)	20 (9.4)	0.29
Committee	23 (4.0)	23 (4.1)	0.95	14 (7.4)	16 (7.5)	0.95

* the 95% Confidence Interval for difference between treatment group percents was 1.5 ± 2.4 (ITT Population) and 3.1 ± 5.2 (TBW Population) for the study site assignments, and 0.1 ± 2.3 (ITT Population) and 0.1 ± 5.1 (TBW Population) when validated by the Steering Committee.

Cross Reference: Data Listing 7 of Case Report Tabulations (NDA Section XI)

Reviewer's Note: Even though there is a numerical tendency in RDS mortality in favor of Infasurf, the statistically significant difference found in the Prophylaxis trial is not seen in the Treatment trial. This could be due to medical circumstances, i.e., surfactant is more effective when given before the establishment of RDS, due to an inappropriate sample size, which was calculated on the basis of air leaks -not RDS mortality, or due to a true difference in the effect of the drugs on this endpoint. The 95% confidence intervals for the difference in RDS mortality between Infasurf and Exosurf in this trial, as presented below, indicates that for the ITT population, Infasurf can be as much as 4% better or as much as 0.8% worse than Exosurf in this endpoint for the study site assignments or as much as 2.4% better or 2.2% worse when validated by the steering committee. This is an endpoint where Exosurf consistently beat placebo in adequate and well controlled studies, with statistically significant differences of 7 and 2% respectively.

Confidence Intervals for mortality due to RDS. ITT population.

	N=570	N=556	P-value	95% CI (Inf-Exo)
RDS Death study sites	20 (3.5%)	28 (5%)	0.21	(-0.039, 0.008) -0.0153 ± .023
RDS Death committee	23 (4%)	23 (4.1%)	0.95	(-0.024, 0.022) -0.001 ± .023

C. Secondary Efficacy And Safety Measures

(1) Total Respiratory Mortality.

Respiratory mortality is defined as all deaths of any respiratory cause excluding RDS, e.g., pulmonary hypoplasia, pneumonia, pulmonary hemorrhage, etc. that occurred to discharge. Total respiratory mortality involves all deaths of any respiratory cause including RDS and its complications.

No statistically significant differences in total respiratory mortality were noted between both treated groups in the ITT population or in birth weight subsets, regardless of place of assignment. TABLE 12 shows respiratory mortality as assessed at study sites and as validated by the RRC.

TABLE 12. Total Respiratory deaths. ITT and TBW Populations- Number (percentage) patients.

Total Respiratory Death	ITT Population (N=1126)			TBW Population (700-1350 g) (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	P-value	Infasurf (N=190)	Exosurf (N=213)	P-value
Study site	29 (5%)	42 (8%)	0.11	16 (8%)	31 (15%)	0.063
Steering committee	32 (6%)	39 (7%)	0.39	19 (10%)	27 (13%)	0.44

Cross Reference: Data Listing 7 of Case Report Tabulations (NDA Section XI)

Reviewer's note: Respiratory mortality, analyzed by age of death, did not show a statistically significant difference between treatment groups. (TABLE 13). When validated by the central committee, 72% of the deaths due to respiratory causes in the Infasurf group and 59% in the Exosurf group in the ITT population occurred within the first 7 days of life (p-value=0.32). In the TBW population, 68% of the deaths due to respiratory causes in the Infasurf group and 59% in the Exosurf group died in the first 7 days of life (p-value=0.55). The difference in respiratory mortality the first 7 days of life follows the same trend when evaluated by the study sites (p-values of 0.21 and 0.53 for the ITT population and the TBW population respectively).

TABLE 13. Total respiratory Mortality by place of determination and age. ITT and TBW population. - Number (percentage) of patients.

Total Respiratory Mortality	ITT population			TBW Population		
	Infasurf (N=570)	Exosurf (N=556)	p-value	Infasurf (N=190)	Exosurf (N=213)	p-value
COMMITTEE*	32/570(5.6)	39/556 (7.0)	.31	19/190 (10)	27/213 (12.6)	.44
≤7 days	23/32 (72)	23/39 (59)	.32	13/19 (68)	16/27 (59)	.55
>7 days	9/32 (28)	16/39 (41)	.32	6/19(31.5)	11/27 (41)	.55
STUDY SITES[a]	28/570 (4.9)	42 /556(7.5)	.06	16/190(8.4)	31/213 (14.5)	.06
≤7 days	20/28 (71)	23/42 (55)	.20	11/16 (69)	17/31 (55)	.53
>7 days	8/28 (28)	19/42 (45)	.20	5/16 (31)	14/31 (45)	.53

[a]Cause of death as assigned by the study sites.
*Cause of death assigned by the central committee.

When assessing the comparability of the above results, we found that the 95% confidence intervals of the difference between Infasurf and Exosurf in total respiratory mortality, as presented below, indicate with 95% confidence that the true difference in respiratory deaths between Infasurf and Exosurf would be between -0.026 and 0.007 when assessed by the study sites or between -0.03 and 0.004 as validated by the steering committee. This would indicate that Infasurf can be as much as 2.6% better or as little as 0.7% worse than Exosurf when assessed by the study site assignments, or as much as 3% better or 0.4% worse than Exosurf when validated by the steering committee.

TABLE 14. CI intervals for Respiratory mortality. ITT population.

	Infasurf N=570	Exosurf N=556	p-value	95% CI (Inf-Exo)
Resp Deaths study sites	29 (5%)	42 (8%)	0.11	(-0.053, 0.0038)
committee	32 (6%)	39 (7%)	0.39	(-0.0424, 0.0144)

(2) Neonatal Mortality

Neonatal mortality is defined as all deaths, of any cause, that occurred during the study period. It was totaled at 7 and 28 days and to discharge.

TABLES 15 and 16 show the number of infants who died per treatment group totalled at 7, 28, and to discharge (from tables 5.24 and 5.25 vol 1.27). No statistically significant differences were found between treatment groups.

TABLE 15. Mortality by age. Number (Percentage) of Patients - ITT and TBW population.

Mortality by Age	ITT Population (N=1126)			TBW Population (700-1350 g) (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value	Infasurf (N=190)	Exosurf (N=213)	p-Value
7 days	34 (6.0)	34 (6.1)	0.91	17 (8.9)	21 (9.9)	0.82
28 days	47 (8.3)	58 (10.4)	0.21	22 (11.6)	33 (15.5)	0.32
to Discharge	52 (9.1)	69 (12.4)	0.07	27 (14.2)	42 (19.7)	0.17

TABLE 16. Mortality by age. Number (Percentage) of Patients - Neonates under 700 g or over 1350 g

Mortality by Cause	Birth Weight Population: <700 g			Birth Weight Population: >1350 g		
	Infasurf (N=36)	Exosurf (N=34)	p-Value	Infasurf (N=344)	Exosurf (N=309)	p-Value
7 days	12 (33.3)	9 (26.5)	0.25	5 (1.5)	4 (1.3)	0.88
28 days	17 (47.2)	13 (38.2)	0.55	8 (2.3)	12 (3.9)	0.26
to Discharge	18 (50.0)	18 (52.9)	0.69	7 (2.0)	9 (2.9)	0.46

Reviewer's note: Mortality for any cause did not show any statistically significant difference between treatment groups. From TABLE 16 it is obvious that the analysis of the total mortality to discharge of the > 1350 g population of the Exosurf group is incorrect, i.e., the table shows that there were more deaths at 28 days than to discharge. There are also other minor errors in the number of deaths in other categories. Reviewing the data we came up with a slightly different table (TABLE 17), where total mortality was identified by period, i.e., events that occurred up to day 7 of life, between 7 and 28 days and between 28 days and discharge. There were no statistically significant differences in mortality by age between both groups in any birth weight subset. This table does not include patients who died after being discharged (4 in the Infasurf and 1 in the Exosurf group).

By using the 95% confidence intervals of the difference between Infasurf and Exosurf on total neonatal mortality, (-0.069, 0.003) we can say that Infasurf can be as much as 7% better or as much as 0.3% worse than Exosurf on this endpoint.

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TABLE 17. Total Mortality by BW and age of patients. Number/total (Percentage) of patients.

Age	INFASURF (N=52)	EXOSURF (N=69)	p-Value*
<7 days	34/52 (65)*	35/69 (51)*	.14
<700 gr.	12/34 (35)	9/35 (26)	
TBW	17/34 (50)	22/35 (63)	
>1350 gr.	5/34 (15)	4/35 (11)	
7 to 28 days	13/52 (25)*	21/69 (30)*	.55
<700 gr.	5/13 (38)	5/21 (24)	
TBW	7/13 (53)	12/21 (57)	
>1350 gr.	1/13 (4)	4/21 (19)	
28 days to D/C	5/52 (10)*	13/69 (19)*	.20
<700 gr.	1/5 (20)	4/13 (30)	
TBW	3/5 (60)	8/13 (61)	
>1350 gr.	1/5 (20)	1/13 (8)	

*Denominator is total of infants who died in each treatment group.
*Fisher's two-tailed test

(3) Incidence of Crossover Surfactant Treatment

Requirements established to be eligible for crossover treatment:

i. The infant had received a full course (2 treatments) of the randomized surfactant,

ii. The a/A PO_2 ratio was $\leq$ 0.10 on two consecutive arterial blood gases obtained more than 4 hours after the final treatment of randomized surfactant, and

iii. The infant was < 96 hours old.

In general, Infasurf-treated patients required crossover therapy less often than Exosurf-treated patients. The differences in crossover rates reached statistical significance in both the ITT and TBW Population subgroups (TABLE 18).

TABLE 18. Patients Who Required Crossover to the Other Surfactant - Number (Percentage) of Patients - ITT and TBW Populations

Variable	Infasurf (N=570)	Exosurf (N=556)	p-Value
ITT Population	36/570 (6.3)	55/556 (9.9)	0.029
<700 grams	3/36 (8.3)	7/34 (20.6)	0.18
700 - 1350 grams (TBW)	14/190 (7.4)	29/213 (13.6)	0.05
>1350 grams	19/344 (5.5)	19/309 (6.1)	0.74

Cross Reference: Data Listing 3 of Case Report Tabulations (NDA Section XI)

Reviewer's note: Not all the patients who were crossed over met the protocol criteria for cross over therapy. We reviewed each child's variables to see if they met the criteria. Forty eight infants missed at least one of the above mentioned criteria for cross over therapy (14 in the Infasurf group and 34 in the Exosurf group). This left a total of 43 infants that met the criteria for cross over (22 Infasurf-treated, and 21 Exosurf-treated infants) with no statistically significant difference between the groups. Table 19 presents the distribution of those infants who were crossed over without meeting the established criteria. Table 20 shows the distribution of infants who did qualify to cross over treatment.

TABLE 19. **Distribution of patients who where crossed over without meeting criteria. Number of patients.**

Birth Weight group	Infasurf	Exosurf
ITT	14	34
TBW	6	19
<700 g	2	6
>1350 g	6	9

TABLE 20. Incidence of Crossovers (qualifying established criteria). Number (Percentage) of patients.

B W group	INFASURF	EXOSURF	p-Value*
ITT	22/570 (4)	21/556 (4)	1
TBW	8/190 (4)	10/210 (5)	.82
< 700 g	1/36 (3)	1/34 (3)	1
> 1350 g	13/344 (4)	10/309 (3)	.83

*Fisher's two tailed test

—(4) Incidence of Acute Pulmonary Hemorrhage

The incidence of acute pulmonary hemorrhage was calculated for the ITT and for the TBW populations. No significant difference in the incidence of acute pulmonary hemorrhage between treatment groups was seen in either the ITT or TBW populations. The incidence of acute pulmonary hemorrhage is presented in Table 21.

TABLE 21. Pulmonary hemorrhages - Number (Percentage) of Patients - ITT and TBW Populations.

Parameter	ITT Population			TBW Population (700-1350 g)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value	Infasurf (N=190)	Exosurf (N=213)	p-Value
Pulmonary Hemorrhage	21(3.7)	23 (4.1)	0.878	16 (8.4)	12 (5.6)	0.328

Cross Reference: Data Listing 8 of Case Report Tabulations (NDA Section XI)

Reviewer's note: The above table represents those events that occurred before the seventh day of life in the ITT and the TBW populations only. We wanted to look at all pulmonary hemorrhages that occurred during the study period in all the subsets. There were a total of 28 cases in the Exosurf group (7 cases occurred at >7 days of age) and 27 cases occurred in the Infasurf group (4 cases occurred at >7 days of age). Table 22 shows the incidence of pulmonary hemorrhages by birth weight. There were no statistically significant differences between the treatment groups.